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(54) Title: METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST

(57) Abstract

A therapeutic method is described for treating cardiofibrosis or cardiac hypertrophy using a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compounds characterized by the presence of a $9\alpha,11\alpha$-substituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.

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METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST

Field of the Invention

Therapeutic methods are described for treatment of cardiofibrosis and cardiac hypertrophy. Of particular interest are therapies using an epoxy-containing steroidal aldosterone receptor antagonist compound such as epoxymexrenone in combination with an angiotensin II receptor antagonist compound.

Background of the Invention

Myocardial (or cardiac) failure, whether a consequence of a previous myocardial infarction, heart disease associated with hypertension, or primary cardiomyopathy, is a major health problem of worldwide proportions. The incidence of symptomatic heart failure has risen steadily over the past several decades.

In clinical terms, decompensated cardiac failure consists of a constellation of signs and symptoms that arises from congested organs and hypoperfused tissues to form the congestive heart failure (CHF) syndrome. Congestion is caused largely by increased venous pressure and by inadequate sodium (Na^+) excretion, relative to dietary Na^+ intake, and is importantly related to circulating levels of aldosterone (ALDO). An abnormal retention of Na^+ occurs via tubular epithelial cells throughout the nephron, including the later portion of the distal tubule and cortical collecting ducts, where ALDO receptor sites are present.

ALDO is the body's most potent mineralocorticoid hormone. As connoted by the term mineralocorticoid, this

steroid hormone has mineral-regulating activity. It promotes Na^+ reabsorption not only in the kidney, but also from the lower gastrointestinal tract and salivary and sweat glands, each of which represents classic ALDO-responsive tissues. ALDO regulates Na^+ and water resorption at the expense of potassium (K^+) and magnesium (Mg^{2+}) excretion.

ALDO can also provoke responses in nonepithelial cells. Elicited by a chronic elevation in plasma ALDO level that is inappropriate relative to dietary Na^+ intake, these responses can have adverse consequences on the structure of the cardiovascular system. Hence, ALDO can contribute to the progressive nature of myocardial failure for multiple reasons.

Multiple factors regulate ALDO synthesis and metabolism, many of which are operative in the patient with myocardial failure. These include renin as well as non-renin-dependent factors (such as K^+, ACTH) that promote ALDO synthesis. Hepatic blood flow, by regulating the clearance of circulating ALDO, helps determine its plasma concentration, an important factor in heart failure characterized by reduction in cardiac output and hepatic blood flow.

The renin-angiotensin-aldosterone system (RAAS) is one of the hormonal mechanisms involved in regulating pressure/volume homeostasis and also in the development of hypertension. Activation of the renin-angiotensin-aldosterone system begins with renin secretion from the juxtaglomerular cells in the kidney and culminates in the formation of angiotensin II, the primary active species of this system. This octapeptide, angiotensin II, is a potent vasoconstrictor and also produces other physiological effects such as stimulating aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, stimulating vasopressin secretion, causing positive cardiac inotropic

effect and modulating other hormonal systems.

Previous studies have shown that antagonizing angiotensin II binding at its receptors is a viable approach to inhibit the renin-angiotensin system, given the pivotal role of this octapeptide which mediates the actions of the renin-angiotensin system through interaction with various tissue receptors. There are several known angiotensin II antagonists, most of which are peptidic in nature. Such peptidic compounds are of limited use due to their lack of oral bioavailability or their short duration of action. Also, commercially-available peptidic angiotensin II antagonists (e.g., Saralasin) have a significant residual agonist activity which further limit their therapeutic application.

Non-peptidic compounds with angiotensin II antagonist properties are known. For example, early descriptions of such non-peptidic compounds include the sodium salt of 2-n-butyl-4-chloro-1-(2-chlorobenzyl)imidazole-5-acetic acid which has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [P. C. Wong et al, J. Pharmacol. Exp. Ther., 247(1), 1-7 (1988)]. Also, the sodium salt of 2-butyl-4-chloro-1-(2-nitrobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [A. T. Chiu et al, European J. Pharmacol., 157, 31-21 (1988)]. A family of 1-benzylimidazole-5-acetate derivatives has been shown to have competitive angiotensin II antagonist properties [A. T. Chiu et al, J. Pharmacol. Exp. Ther., 250(3), 867-874 (1989)]. U.S. Patent No. 4,816,463 to Blankey et al describes a family of 4,5,6,7-tetrahydro-1H-imidazo(4,5-c)-tetrahydro-pyridine derivatives useful as antihypertensives, some of which are reported to antagonize the binding of labelled angiotensin II to rat adrenal receptor preparation and thus cause a significant

decrease in mean arterial blood pressure in conscious hypertensive rats. Other families of non-peptidic angiotensin II antagonists have been characterized by molecules having a biphenylmethyl moiety attached to a heterocyclic moiety. For example, EP No. 253,310, published 20 January 1988, describes a series of aralkyl imidazole compounds, including in particular a family of biphenylmethyl substituted imidazoles, as antagonists to the angiotensin II receptor. EP No. 323,841 published 12 July 1989 describes four classes of angiotensin II antagonists, namely, biphenylmethylpyrroles, biphenylmethylpyrazoles, biphenylmethyl-1,2,3-triazoles and biphenylmethyl 4-substituted-4H-1,2,4-triazoles, including the compound 3,5-dibutyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-4H-1,2,4-triazole. U.S. Patent No. 4,880,804 to Carini et al describes a family of biphenylmethylbenzimidazole compounds as angiotensin II receptor blockers for use in treatment of hypertension and congestive heart failure.

Many aldosterone receptor blocking drugs are known. For example, spironolactone is a drug which acts at the mineralocorticoid receptor level by competitively inhibiting aldosterone binding. This steroidal compound has been used for blocking aldosterone-dependent sodium transport in the distal tubule of the kidney in order to reduce edema and to treat essential hypertension and primary hyperaldosteronism [F. Mantero et al, Clin. Sci. Mol. Med., 45 (Suppl 1), 219s-224s (1973)]. Spironolactone is also used commonly in the treatment of other hyperaldosterone-related diseases such as liver cirrhosis and congestive heart failure [F.J. Saunders et al, Aldactone; Spironolactone: A Comprehensive Review, Searle, New York (1978)]. Progressively-increasing doses of spironolactone from 1 mg to 400 mg per day [i.e., 1 mg/day, 5 mg/day, 20 mg/day] were administered to a spironolactone-intolerant patient to treat cirrhosis-related ascites [P.A. Greenberger et al, N. Eng. Reg. Allergy Proc., 7(4), 343-345 (Jul-Aug, 1986)]. It has been recognized that development of

myocardial fibrosis is sensitive to circulating levels of both Angiotensin II and aldosterone, and that the aldosterone antagonist spironolactone prevents myocardial fibrosis in animal models, thereby linking aldosterone to excessive collagen deposition [D. Klug et al, Am. J. Cardiol., 71 (3), 46A-54A (1993)]. Spironolactone has been shown to prevent fibrosis in animal models irrespective of the development of left ventricular hypertrophy and the presence of hypertension [C.G. Brilla et al, J. Mol. Cell. Cardiol., 25(5), 563-575 (1993)]. Spironolactone at a dosage ranging from 25 mg to 100 mg daily is used to treat diuretic-induced hypokalemia, when orally-administered potassium supplements or other potassium-sparing regimens are considered inappropriate [Physicians' Desk Reference, 46th Edn., p. 2153, Medical Economics Company Inc., Montvale, N.J. (1992)].

Previous studies have shown that inhibiting ACE inhibits the renin-angiotensin system by substantially complete blockade of the formation of angiotensin II. Many ACE inhibitors have been used clinically to control hypertension. While ACE inhibitors may effectively control hypertension, side effects are common including chronic cough, skin rash, loss of taste sense, proteinuria and neutropenia.

Moreover, although ACE inhibitors effectively block the formation of angiotensin II, aldosterone levels are not well controlled in certain patients having cardiovascular diseases. For example, despite continued ACE inhibition in hypertensive patients receiving captopril, there has been observed a gradual return of plasma aldosterone to baseline levels [J. Staessen et al, J. Endocrinol., 91, 457-465 (1981)]. A similar effect has been observed for patients with myocardial infarction receiving zofenopril [C. Borghi et al, J. Clin. Pharmacol., 33, 40-45 (1993)]. This phenomenon has been termed "aldosterone escape".

Another series of steroidal-type aldosterone receptor antagonists is exemplified by epoxy-containing spironolactone derivatives. For example, U.S. Patent No. 4,559,332 issued to Grob et al describes 9α,11α-epoxy-containing spironolactone derivatives as aldosterone antagonists useful as diuretics. These 9α,11α-epoxy steroids have been evaluated for endocrine effects in comparison to spironolactone [M. de Gasparo et al, J. Pharm. Exp. Ther., 240(2), 650-656 (1987)].

Combinations of an aldosterone antagonist and an ACE inhibitor have been investigated for treatment of heart failure. It is known that mortality is higher in patients with elevated levels of plasma aldosterone and that aldosterone levels increase as CHF progresses from activation of the Renin-Angiontensin-Aldosterone System (RAAS). Routine use of a diuretic may further elevate aldosterone levels. ACE inhibitors consistently inhibit angiotensin II production but exert only a mild and transient antialdosterone effect.

Combining an ACE inhibitor and spironolactone has been suggested to provide substantial inhibition of the entire RAAS. For example, a combination of enalapril and spironolactone has been administered to ambulatory patients with monitoring of blood pressure [P. Poncelet et al, Am. J. Cardiol., 65(2), 33K-35K (1990)]. In a 90-patient study, a combination of captopril and spironolactone was administered and found effective to control refractory CHF without serious incidents of hyperkalemia [U. Dahlstrom et al, Am. J. Cardiol., 71, 29A-33A (21 Jan 1993)]. Spironolactone coadministered with an ACE inhibitor was reported to be highly effective in 13 of 16 patients afflicted with congestive heart failure [A.A. van Vliet et al, Am. J. Cardiol., 71, 21A-28A (21 Jan 1993)]. Clinical improvements have been reported for patients receiving a co-therapy of spironolactone and the ACE inhibitor enalapril, although this report mentions that controlled trials are needed to

determine the lowest effective doses and to identify which patients would benefit most from combined therapy [F. Zannad, Am. J. Cardiol., 71(3), 34A-39A (1993)].

Combinations of an angiotensin II receptor antagonist and aldosterone receptor antagonist, are known. For example, PCT Application No. US91/09362 published 25 June 1992 describes treatment of hypertension using a combination of an imidazole-containing angiotensin II antagonist compound and a diuretic such as spironolactone.

Summary of the Invention

A therapeutic method for treating or preventing the progression of cardiofibrosis or cardiac hypertrophy is provided by a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist.

The phrase "angiotensin II receptor antagonist" is intended to embrace one or more compounds or agents having the ability to interact with a receptor site located on various human body tissues, which site is a receptor having a relatively high affinity for angiotensin II and which receptor site is associated with mediating one or more biological functions or events such as vasoconstriction or vasorelaxation, kidney-mediated sodium and fluid retention, sympathetic nervous system activity, and in modulating secretion of various substances such as aldosterone, vasopressin and renin, to lower blood pressure in a subject susceptible to or afflicted with elevated blood pressure. Interactions of such angiotensin II receptor antagonist with this receptor site may be characterized as being either "competitive" (i.e., "surmountable") or as being "insurmountable". These terms, "competitive" and "insurmountable", characterize the relative rates, faster for the former term and slower for the latter term, at which the antagonist compound dissociates from binding with the receptor site.

The phrase "epoxy-steroidal aldosterone receptor antagonist" is intended to embrace one or more agents or compounds characterized by a steroid-type nucleus and having an epoxy moiety attached to the nucleus and which agent or compound binds to the aldosterone receptor, as a competitive inhibitor of the action of aldosterone itself at the receptor site, so as to modulate the receptor-mediated activity of aldosterone.

The phrase "combination therapy", in defining use of an angiotensin II antagonist and an epoxy-steroidal aldosterone receptor antagonist, is intended to embrace administration of each antagonist in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended to embrace co-administration of the antagonist agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each antagonist agent.

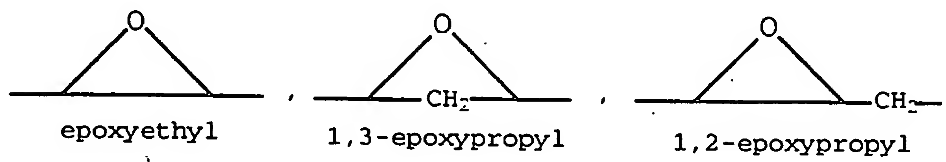
The phrase "therapeutically-effective" is intended to qualify the amount of each antagonist agent for use in the combination therapy which will improve cardiac sufficiency by reducing or preventing the progression of myocardial fibrosis or cardiac hypertrophy.

Another combination therapy of interest would consist essentially of three active agents, namely, an AII antagonist, an aldosterone receptor antagonist agent and a diuretic.

For a combination of AII antagonist agent and an ALDO antagonist agent, the agents would be used in combination in a weight ratio range from about 0.5-to-one to about twenty-to-one of the AII antagonist agent to the aldosterone receptor antagonist agent. A preferred range of these two agents (AII antagonist-to-ALDO antagonist) would be from about one-to-one to about fifteen-to-one, while a more preferred range would be from about one-to-one to about five-to-one, depending ultimately on the selection of the AII antagonist and ALDO antagonist. The diuretic agent may be present in a ratio range of 0.1-to-one to about ten to one (AII antagonist to diuretic).

Detailed Description of the Invention

Epoxy-steroidal aldosterone receptor antagonist compounds suitable for use in the combination therapy consist of these compounds having a steroidal nucleus substituted with an epoxy-type moiety. The term "epoxy-type" moiety is intended to embrace any moiety characterized in having an oxygen atom as a bridge between two carbon atoms, examples of which include the following moieties:



The term "steroidal", as used in the phrase "epoxy-steroidal", denotes a nucleus provided by a cyclopentenophenanthrene moiety, having the conventional "A", "B", "C" and "D" rings. The epoxy-type moiety may be attached to the cyclopentenophenanthrene nucleus at any attachable or substitutable positions, that is, fused to one of the rings of the steroidal nucleus or the moiety may be substituted on a ring member of the ring system. The phrase "epoxy-steroidal" is intended to embrace a steroidal nucleus having one or a plurality of epoxy-type moieties attached thereto.

Epoxy-steroidal aldosterone receptor antagonists suitable for use in combination therapy include a family of compounds having an epoxy moiety fused to the "C" ring of the steroidal nucleus. Especially preferred are 20-spiroxane compounds characterized by the presence of a 9α,11α-substituted epoxy moiety. Table I, below, describes a series of 9α,11α-epoxy-steroidal compounds which may be used in the combination therapy. These epoxy steroids may be prepared by procedures described in U.S. Patent No. 4,559,332 to Grob et al issued 17 December 1985.

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
1		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,γ-lactone, methyl ester, (7α,11.α.,17α)-
2		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester,(7α,11α,17α)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
3		3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,γ-lactone,(6β,7β,11β,17β)-
4		Pregn-4-ene-7,21-dicarboxylic acid,9,11-epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester, monopotassium salt,(7a,11a,17a)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
5		Pregn-4-ene-7,21-dicarboxylic acid,9,11,-epoxy-17-hydroxy-3-oxo-,7-methyl ester, monopotassium salt, (7a,11a,17a)-
6		3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,g-lactone(6a,7a,11.a)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
7		3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxyli acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6a,7a,11a,17a)-
8		3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxyli acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6a,7a,11a,17a)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
9		3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxyli acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,g lactone, (6a,7a,11a.,17a)-
10		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,g-lactone, ethyl ester, (7a,11a,17a)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
11		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,g-lactone, 1-methylethyl ester,(7a,11a,17a)-

Angiotensin II receptor antagonist compounds suitable for use in the combination therapy are described in Table II, below. Preferred compounds for use in the combination therapy may be generally characterized structurally as having two portions. A first portion constitutes a mono-aryl-alkyl moiety, or a bi-aryl-alkyl moiety, or a mono-heteroaryl-alkyl moiety, or a bi-heteroaryl-alkyl moiety. A second portion constitutes a heterocyclic moiety or an open chain hetero-atom-containing moiety.

Typically, the first-portion mono/bi-aryl/heteroaryl-alkyl moiety is attached to the second portion heterocyclic/open-chain moiety through the alkyl group of the mono/bi-aryl/heteroaryl-alkyl moiety to any substitutable position on the heterocyclic/open-chain moiety second portion. Suitable first-portion mono/bi-aryl/heteroaryl-alkyl moieties are defined by any of the various moieties listed under Formula I:

Ar-Alk-L
Ar-L-Ar-Alk-L
Het-L-Ar-Alk-L
Het-L-Het-Alk-L (I)
Ar-L-Het-Alk-L
Het-L-Alk-L

wherein the abbreviated notation used in the moieties of Formula I is defined as follows:

"Ar" means a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being typically fully unsaturated but which also may be partially or fully saturated. "Phenyl" radical most typically exemplifies "Ar".

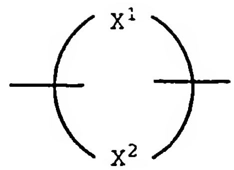
"Het" means a monocyclic or bicyclic fused ring

system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as ring members.

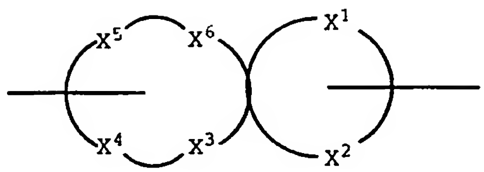
"Alk" means an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms. Typically, "Alk" means "methylene", i.e., $-CH_2-$.

"L" designates a single bond or a bivalent linker moiety selected from carbon, oxygen and sulfur. When "L" is carbon, such carbon has two hydrido atoms attached thereto.

Suitable second-portion heterocyclic moieties of the angiotensin II antagonist compounds, for use in the combination therapy, are defined by any of the various moieties listed under Formula IIa or IIb:



(IIa)



(IIb)

wherein each of X^1 through X^6 is selected from -CH=, $-CH_2-$, -N=, -NH-, O, and S, with the proviso that at least one of X^1 through X^6 in each of Formula IIa and Formula IIb must be a hetero atom. The heterocyclic moiety of Formula IIa or IIb may be attached through a bond from any ring member of the Formula IIa or IIb heterocyclic moiety having a substitutable or a bond-forming position.

Examples of monocyclic heterocyclic moieties of Formula IIa include thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl, isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl, 1,4-pyranyl, 1,2-pyronyl, 1,4-pyronyl, pyridinyl, piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl,

1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

Examples of bicyclic heterocyclic moieties of Formula IIb include benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl, 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiolo-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and 4H-1,3-dioxolo[4,5-d]imidazolyl.

The angiotensin II receptor antagonist compounds, as provided by the first-and-second-portion moieties of Formula I and II, are further characterized by an acidic moiety attached to either of said first-and-second-portion moieties. Preferably this acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:

$$-U_nA \qquad \text{(III)}$$

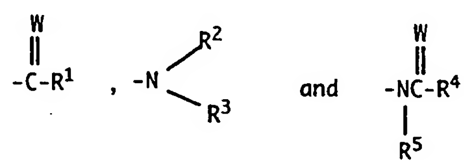
wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms.

The phrase "acidic group selected to contain at least one acidic hydrogen atom", as used to define the $-U_nA$

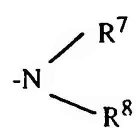
moiety, is intended to embrace chemical groups which, when attached to any substitutable position of the Formula I-IIa/b moiety, confers acidic character to the compound of Formula I-IIa/b. "Acidic character" means proton-donor capability, that is, the capacity of the compound of Formula I-IIa/b to be a proton donor in the presence of a proton-receiving substance such as water. Typically, the acidic group should be selected to have proton-donor capability such that the product compound of Formula I-IIa/b has a pK_a in a range from about one to about twelve. More typically, the Formula I-IIa/b compound would have a pK_a in a range from about two to about seven. An example of an acidic group containing at least one acidic hydrogen atom is carboxyl group (-COOH). Where n is zero and A is -COOH, in the $-U_nA$ moiety, such carboxyl group would be attached directly to one of the Formula I-IIa/b positions. The Formula I-IIa/b compound may have one $-U_nA$ moiety attached at one of the Formula I-IIa/b positions, or may have a plurality of such $-U_nA$ moieties attached at more than one of the Formula I-IIa/b positions. There are many examples of acidic groups other than carboxyl group, selectable to contain at least one acidic hydrogen atom. Such other acidic groups may be collectively referred to as "bioisosteres of carboxylic acid" or referred to as "acidic bioisosteres". Specific examples of such acidic bioisosteres are described hereinafter. Compounds of Formula I-IIa/b may have one or more acidic protons and, therefore, may have one or more pK_a values. It is preferred, however, that at least one of these pK_a values of the Formula I-IIa/b compound as conferred by the $-U_nA$ moiety be in a range from about two to about seven. The $-U_nA$ moiety may be attached to one of the Formula I-IIa/b positions through any portion of the $-U_nA$ moiety which results in a Formula I-IIa/b compound being relatively stable and also having a labile or acidic proton to meet the foregoing pK_a criteria. For example, where the $-U_nA$ acid moiety is tetrazole, the tetrazole is typically attached at

the tetrazole ring carbon atom.

For any of the moieties embraced by Formula I and Formula II, such moieties may be substituted at any substitutable position by one or more radicals selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula

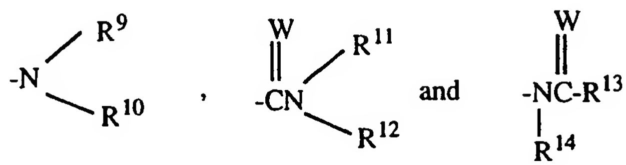


wherein W is oxygen atom or sulfur atom; wherein each of R^1 through R^5 is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR^6 and



wherein Y is selected from oxygen atom and sulfur atom and R^6 is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^1, R^2, R^3, R^4, R^5, R^7 and R^8 is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl,

arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^1, R^2, R^3, R^4, R^5, R^7 and R^8 is further independently selected from amino and amido radicals of the formula



wherein W is oxygen atom or sulfur atom; wherein each of R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl; and wherein each of R^2 and R^3 taken together and each of R^4 and R^5 taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein each of R^2 and R^3 taken together and each of R^7 and R^8 taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

The combination therapy of the invention would be useful in treating myocardial fibrosis or cardiac hypertrophy, particularly left ventricular hypertrophy. The combination therapy would also be useful with adjunctive therapies. For example, the combination therapy may be used in combination with other drugs, such as a diuretic, to aid

in treatment of hypertension.

Table II, below, contains description of angiotensin II antagonist compounds which may be used in the combination therapy. Associated with each compound listed in Table II is a published patent document describing the chemical preparation of the angiotensin II antagonist compound as well as the biological properties of such compound. The content of each of these patent documents is incorporated herein by reference.

TABLE II: Angiotensin II Antagonists

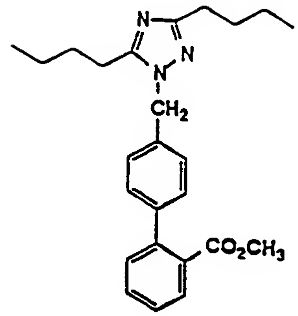
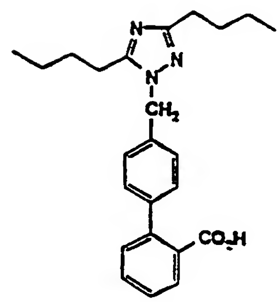
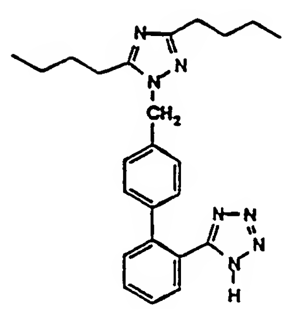
Compound #	Structure	Source
1		WO #91/17148 pub. 14 Nov 91
2		WO #91/17148 pub. 14 Nov 91
3		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

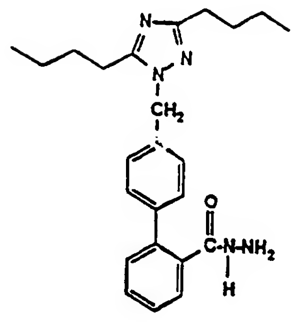
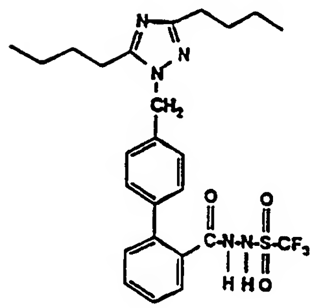
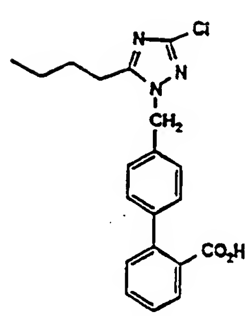
Compound #	Structure	Source
4		WO #91/17148 pub. 14 Nov 91
5		WO #91/17148 pub. 14 Nov 91
6		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

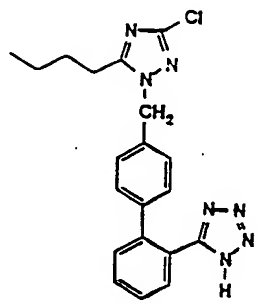
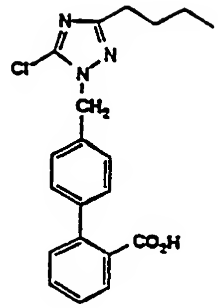
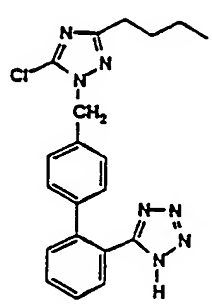
Compound #	Structure	Source
7		WO #91/17148 pub. 14 Nov 91
8		WO #91/17148 pub. 14 Nov 91
9		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

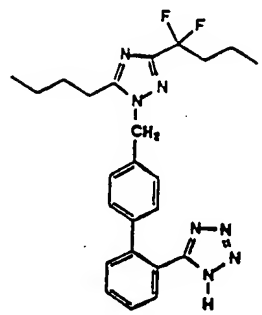
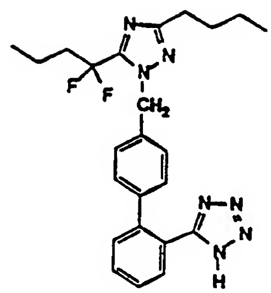
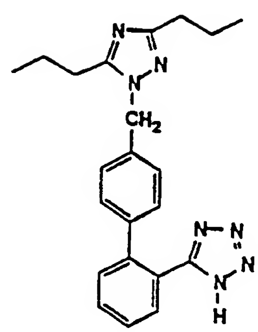
Compound #	Structure	Source
10		WO #91/17148 pub. 14 Nov 91
11		WO #91/17148 pub. 14 Nov 91
12		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

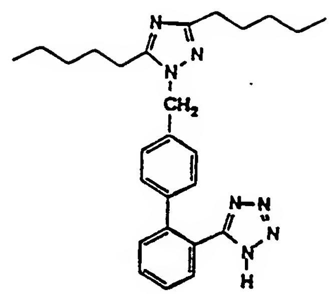
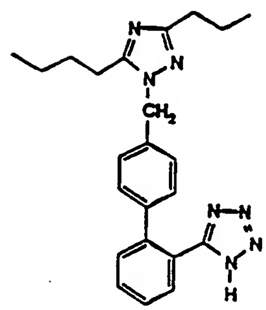
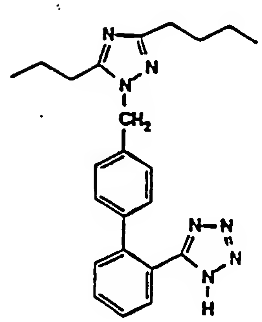
Compound #	Structure	Source
13		WO #91/17148 pub. 14 Nov 91
14		WO #91/17148 pub. 14 Nov 91
15		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

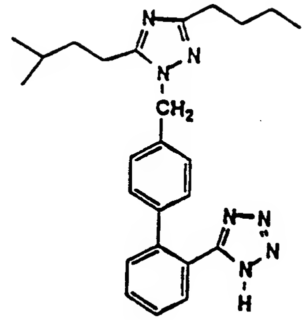
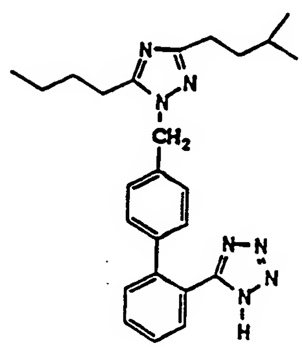
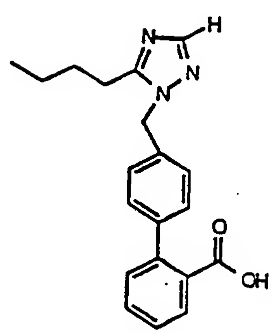
Compound #	Structure	Source
16		WO #91/17148 pub. 14 Nov 91
17		WO #91/17148 pub. 14 Nov 91
18		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

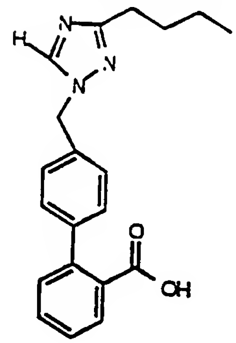
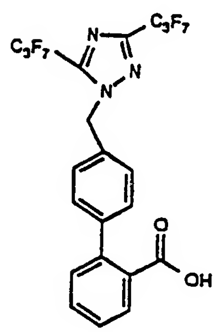
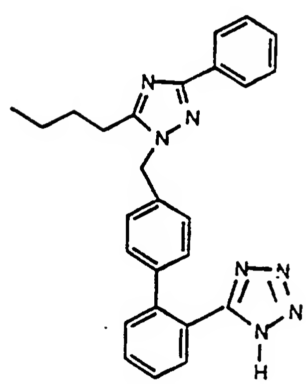
Compound #	Structure	Source
19		WO #91/17148 pub. 14 Nov 91
20		WO #91/17148 pub. 14 Nov 91
21		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

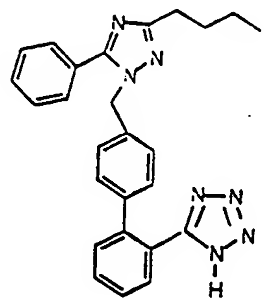
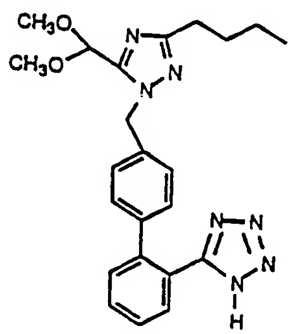
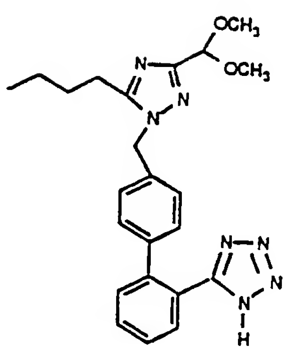
Compound #	Structure	Source
22		WO #91/17148 pub. 14 Nov 91
23		WO #91/17148 pub. 14 Nov 91
24		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

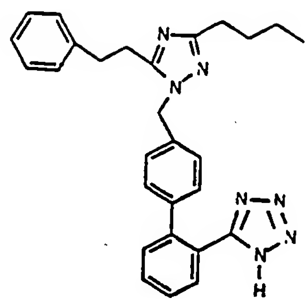
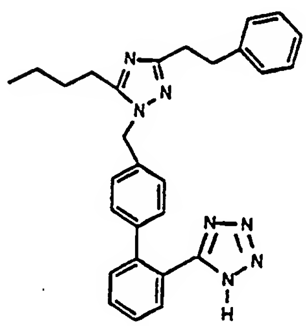
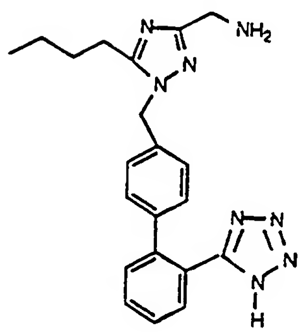
Compound #	Structure	Source
25		WO #91/17148 pub. 14 Nov 91
26		WO #91/17148 pub. 14 Nov 91
27		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

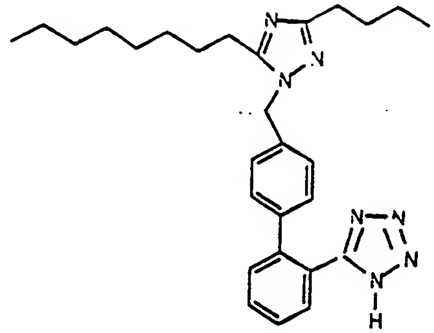
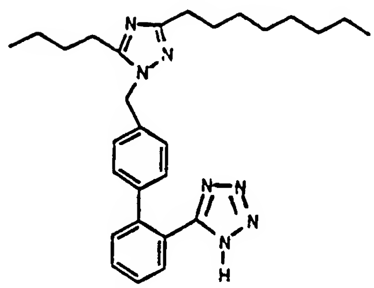
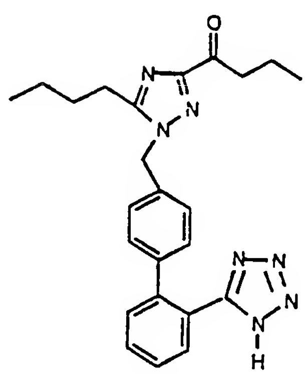
Compound #	Structure	Source
28		WO #91/17148 pub. 14 Nov 91
29		WO #91/17148 pub. 14 Nov 91
30		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

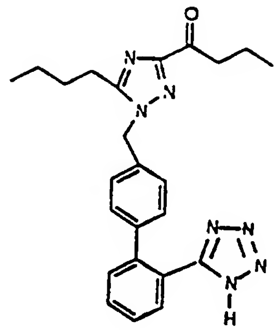
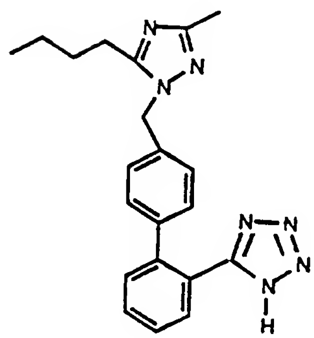
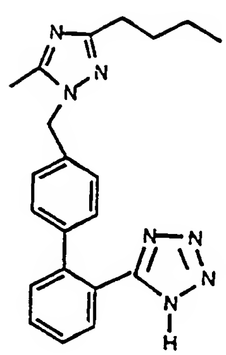
Compound #	Structure	Source
31		WO #91/17148 pub. 14 Nov 91
32		WO #91/17148 pub. 14 Nov 91
33		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

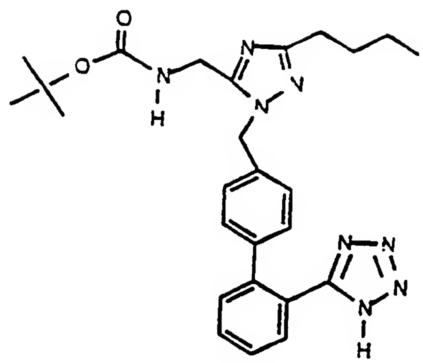
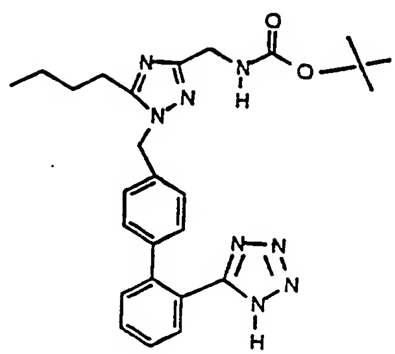
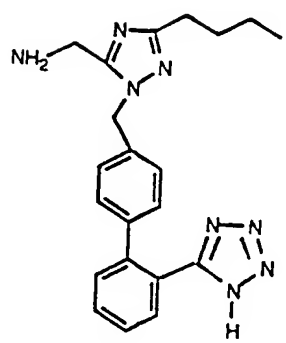
Compound #	Structure	Source
34		WO #91/17148 pub. 14 Nov 91
35		WO #91/17148 pub. 14 Nov 91
36		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

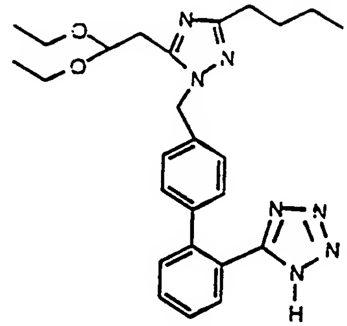
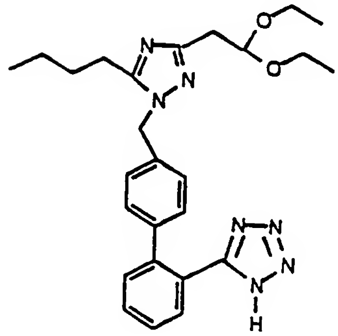
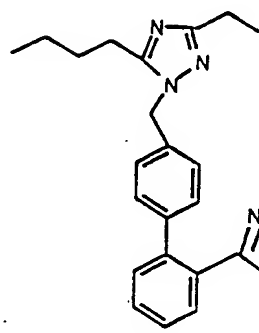
Compound #	Structure	Source
37		WO #91/17148 pub. 14 Nov 91
38		WO #91/17148 pub. 14 Nov 91
39		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

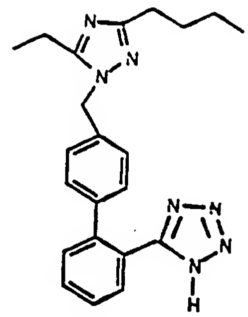
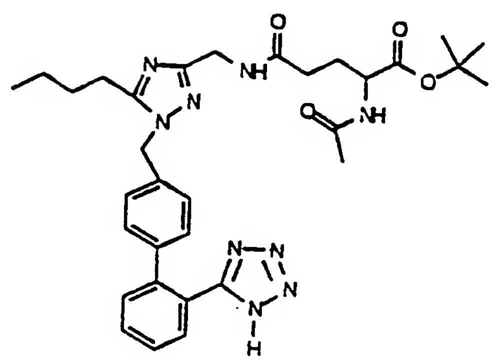
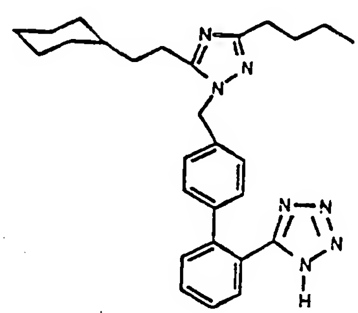
Compound #	Structure	Source
40		WO #91/17148 pub. 14 Nov 91
41		WO #91/17148 pub. 14 Nov 91
42		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

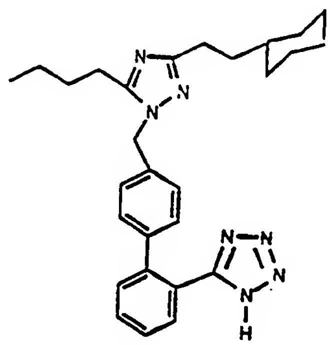
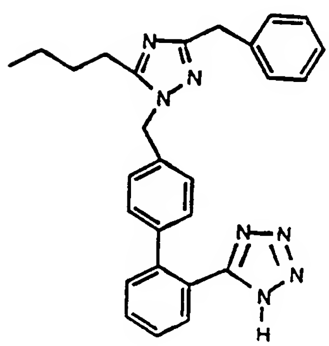
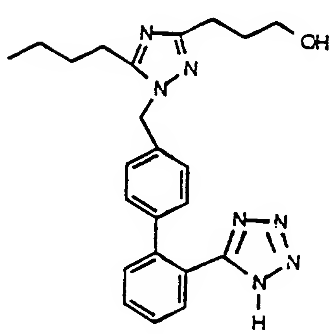
Compound #	Structure	Source
43		WO #91/17148 pub. 14 Nov 91
44		WO #91/17148 pub. 14 Nov 91
45		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

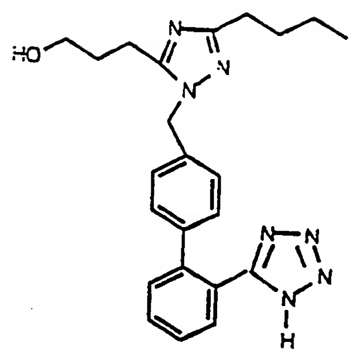
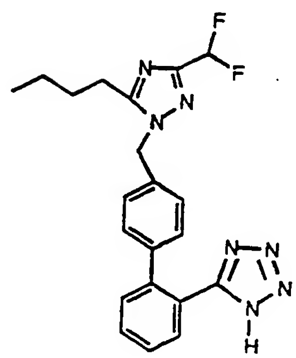
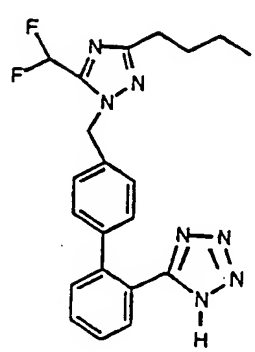
Compound #	Structure	Source
46		WO #91/17148 pub. 14 Nov 91
47		WO #91/17148 pub. 14 Nov 91
48		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

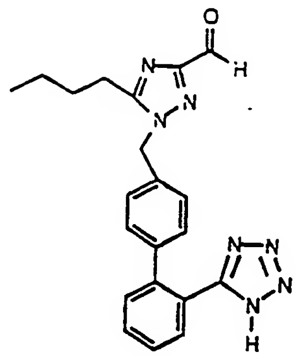
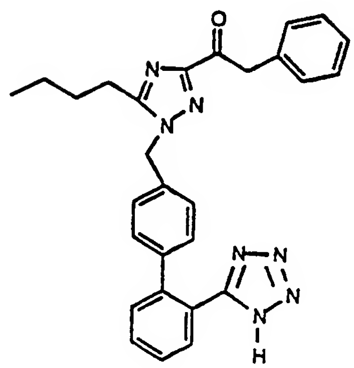
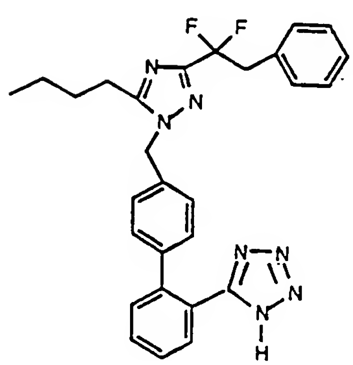
Compound #	Structure	Source
49		WO #91/17148 pub. 14 Nov 91
50		WO #91/17148 pub. 14 Nov 91
51		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

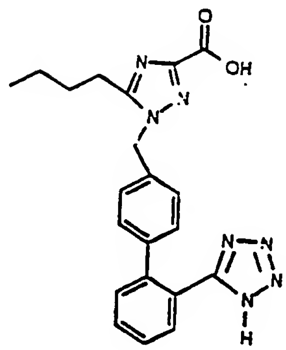
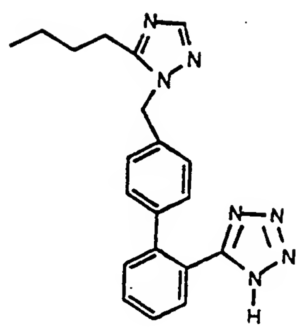
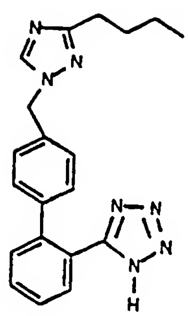
Compound #	Structure	Source
52		WO #91/17148 pub. 14 Nov 91
53		WO #91/17148 pub. 14 Nov 91
54		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

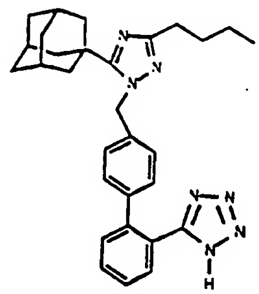
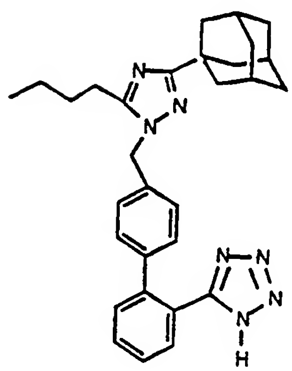
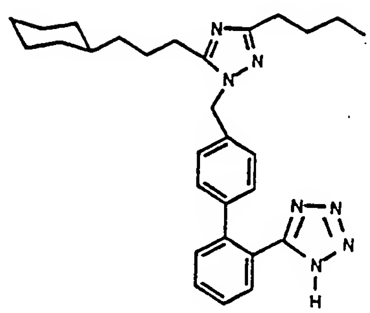
Compound #	Structure	Source
55		WO #91/17148 pub. 14 Nov 91
56		WO #91/17148 pub. 14 Nov 91
57		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

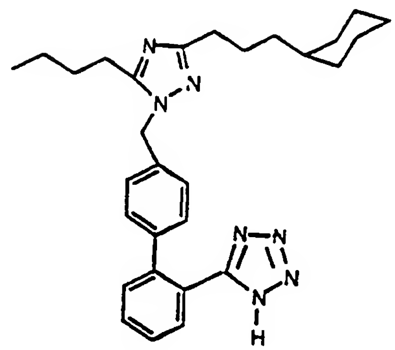
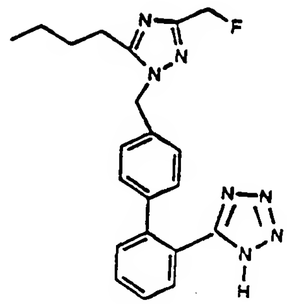
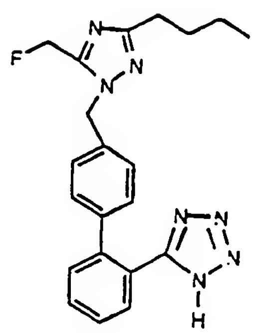
Compound #	Structure	Source
58		WO #91/17148 pub. 14 Nov 91
59		WO #91/17148 pub. 14 Nov 91
60		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

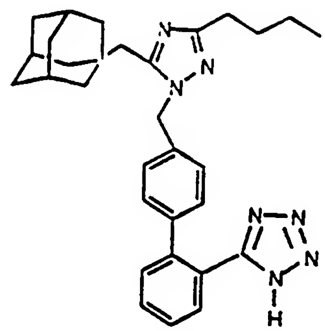
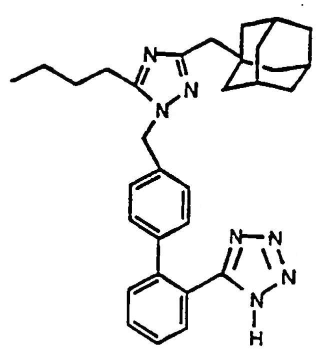
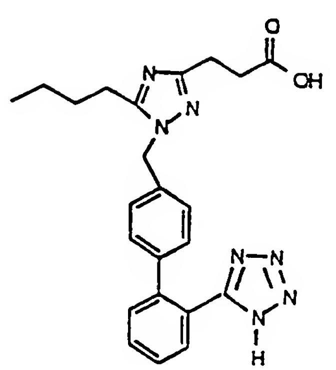
Compound #	Structure	Source
61		WO #91/17148 pub. 14 Nov 91
62		WO #91/17148 pub. 14 Nov 91
63		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

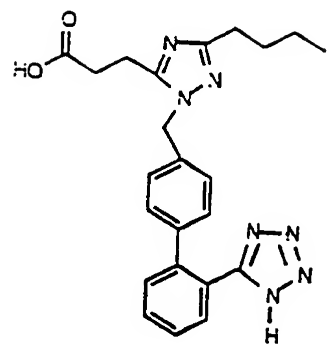
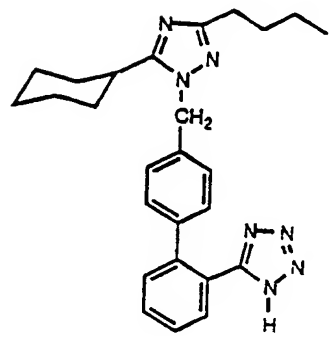
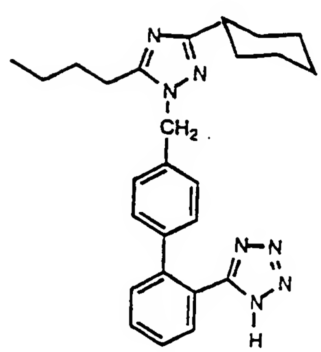
Compound #	Structure	Source
64		WO #91/17148 pub. 14 Nov 91
65		WO #91/17148 pub. 14 Nov 91
66		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

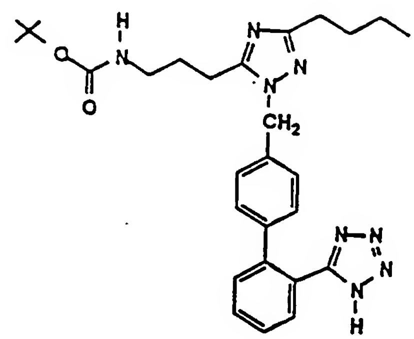
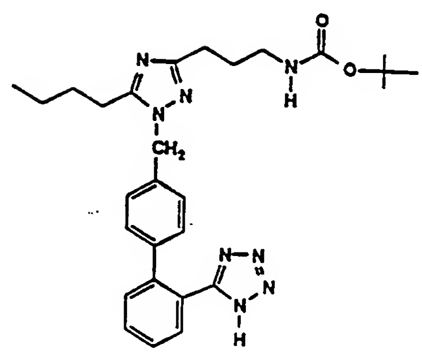
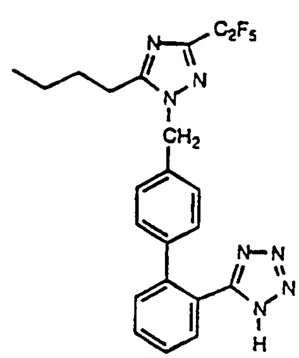
Compound #	Structure	Source
67		WO #91/17148 pub. 14 Nov 91
68		WO #91/17148 pub. 14 Nov 91
69		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

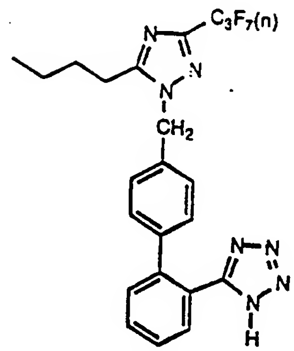
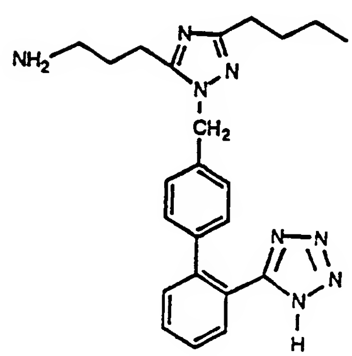
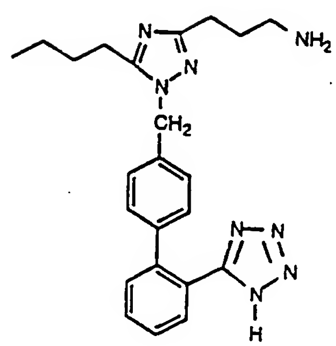
Compound #	Structure	Source
70		WO #91/17148 pub. 14 Nov 91
71		WO #91/17148 pub. 14 Nov 91
72		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

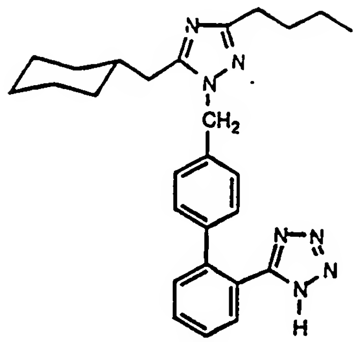
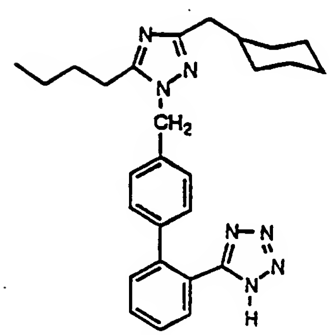
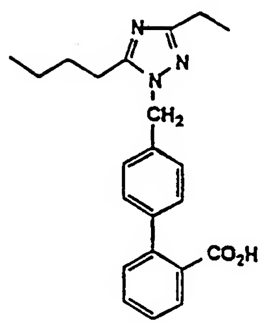
Compound #	Structure	Source
73		WO #91/17148 pub. 14 Nov 91
74		WO #91/17148 pub. 14 Nov 91
75		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

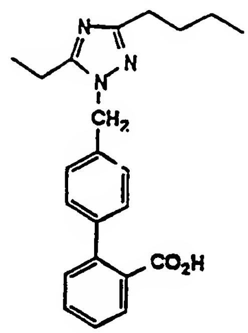
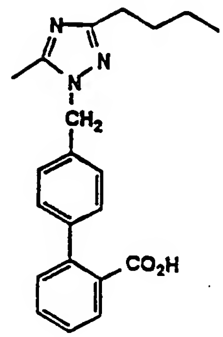
Compound #	Structure	Source
76		WO #91/17148 pub. 14 Nov 91
77		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

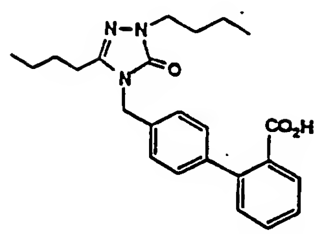
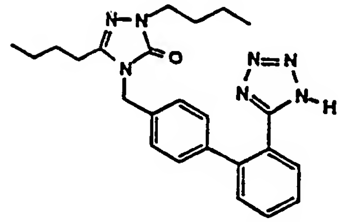
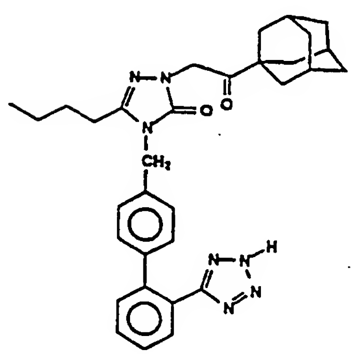
Compound #	Structure	Source
78		WO #91/18888 pub.
79		WO #91/18888 pub.
80		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

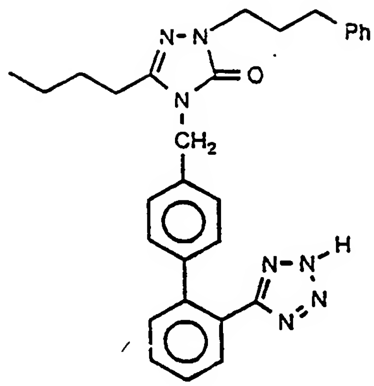
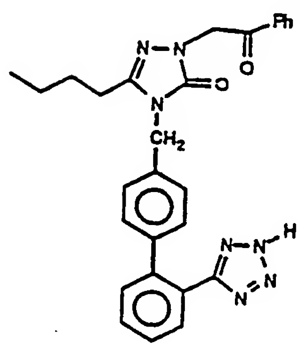
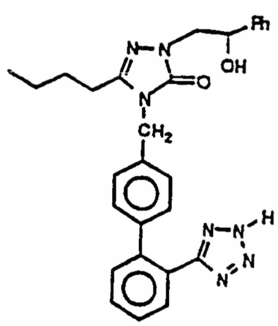
Compound #	Structure	Source
81		WO #91/18888 pub.
82		WO #91/18888 pub.
83		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

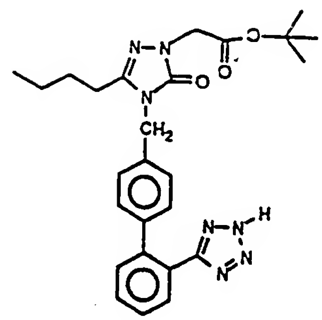
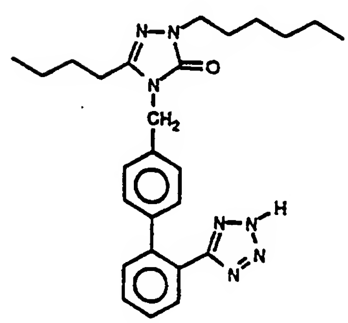
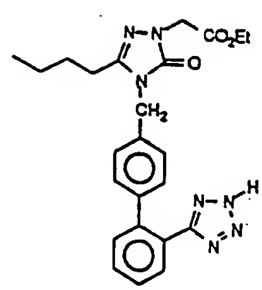
Compound #	Structure	Source
84		WO #91/18888 pub.
85		WO #91/18888 pub.
86		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

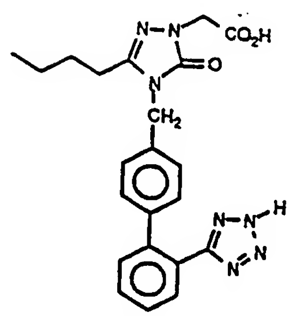
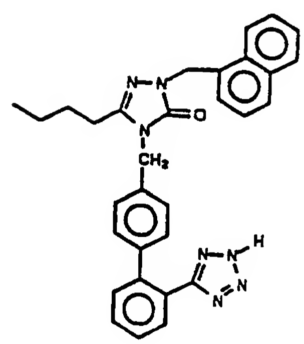
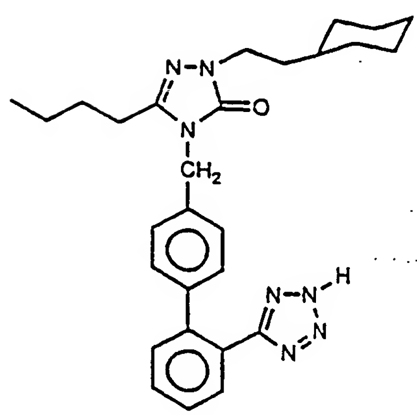
Compound #	Structure	Source
87		WO #91/18888 pub.
88		WO #91/18888 pub.
89		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

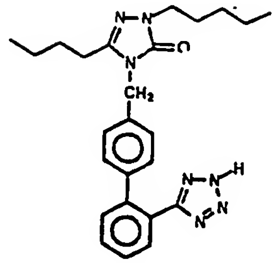
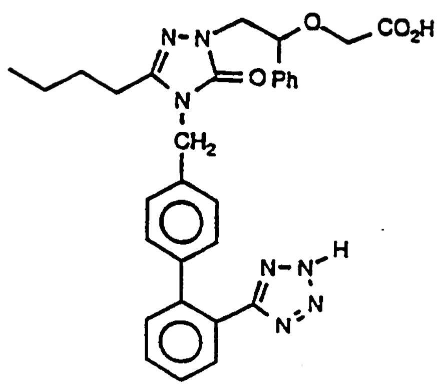
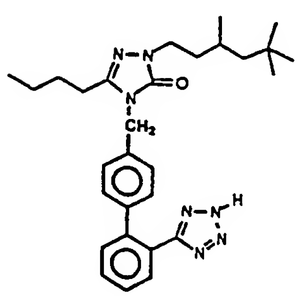
Compound #	Structure	Source
90		WO #91/18888 pub.
91		WO #91/18888 pub.
92		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

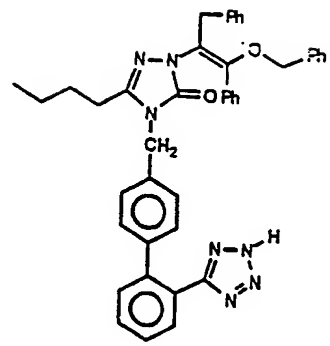
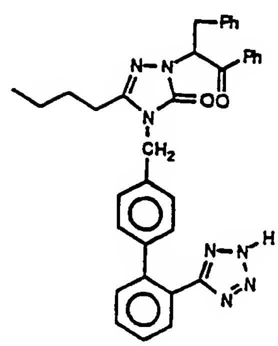
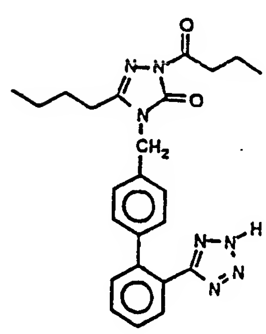
Compound #	Structure	Source
93		WO #91/18888 pub.
94		WO #91/18888 pub.
95		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

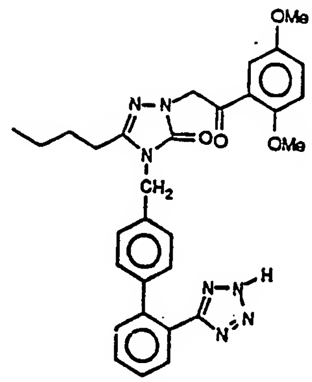
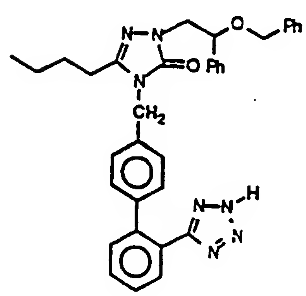
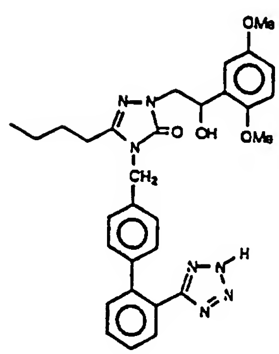
Compound #	Structure	Source
96		WO #91/18888 pub.
97		WO #91/18888 pub.
98		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

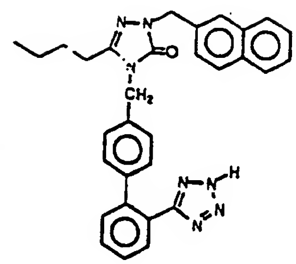
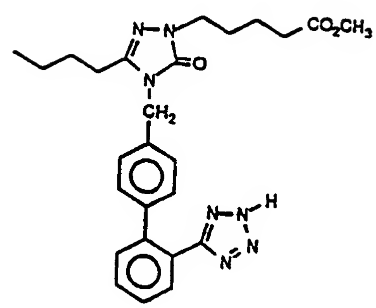
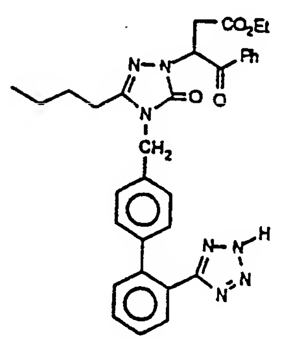
Compound #	Structure	Source
99		WO #91/18888 pub.
100		WO #91/18888 pub.
101		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

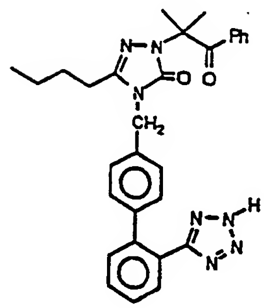
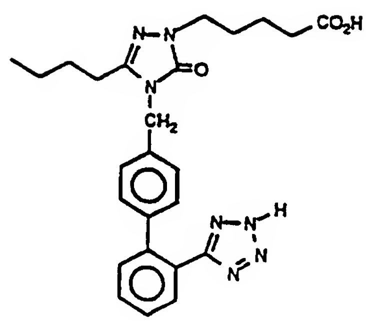
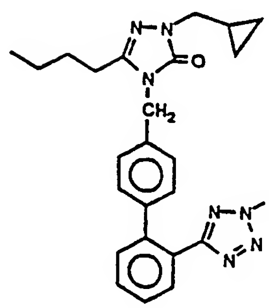
Compound #	Structure	Source
102		WO #91/18888 pub.
103		WO #91/18888 pub.
104		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

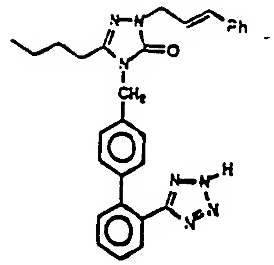
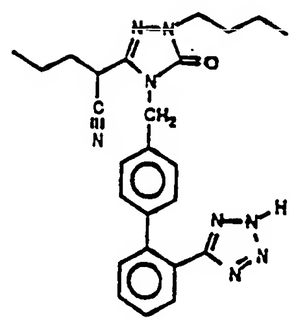
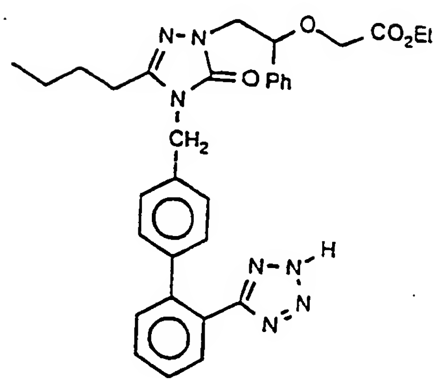
Compound #	Structure	Source
105		WO #91/18888 pub.
106		WO #91/18888 pub.
107		WO #91/18888 pub.

TABLE II: Angiotensin II Antagonists

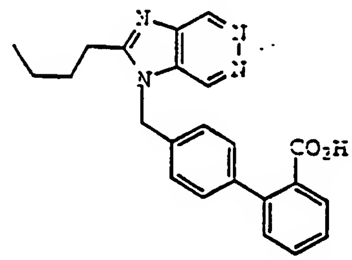
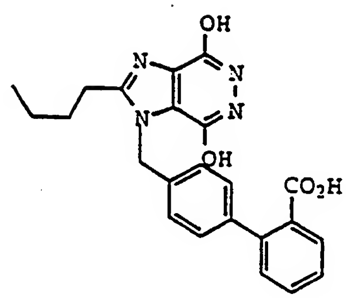
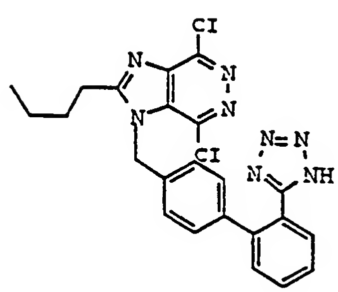
Compound #	Structure	Source
108		WO #91/19715 pub. 26 Dec 91
109		WO #91/19715 pub. 26 Dec 91
110		WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

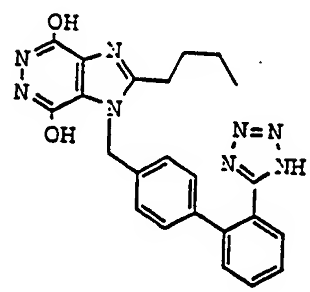
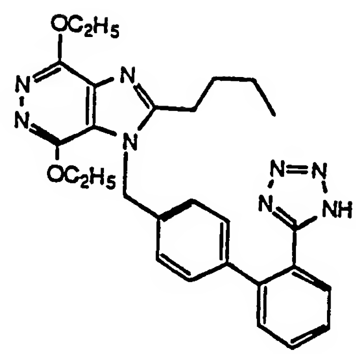
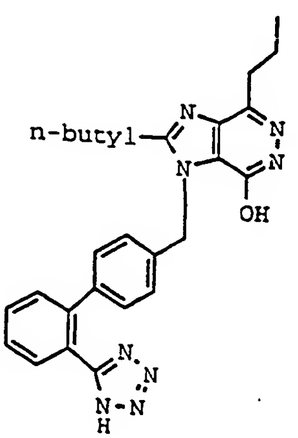
Compound #	Structure	Source
111		WO #91/19715 pub. 26 Dec 91
112		WO #91/19715 pub. 26 Dec 91
113		WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

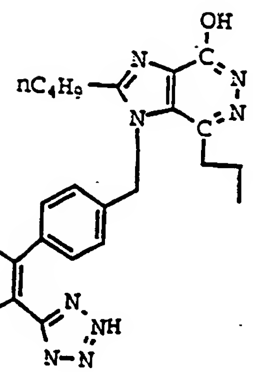
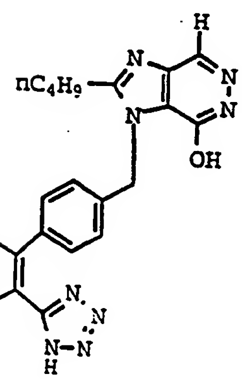
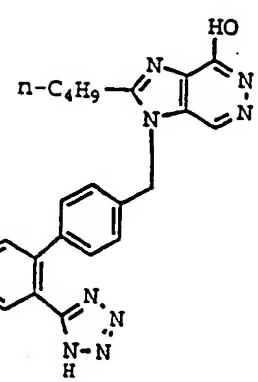
Compound #	Structure	Source
114		WO #91/19715 pub. 26 Dec 91
115		WO #91/19715 pub. 26 Dec 91
116		WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

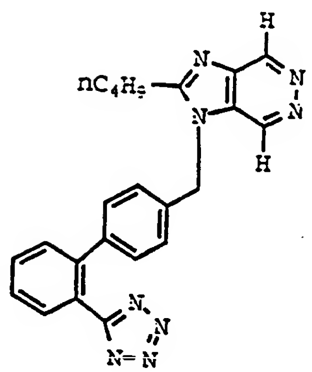
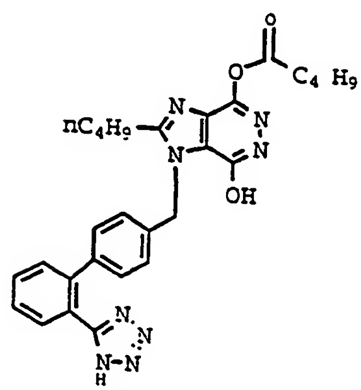
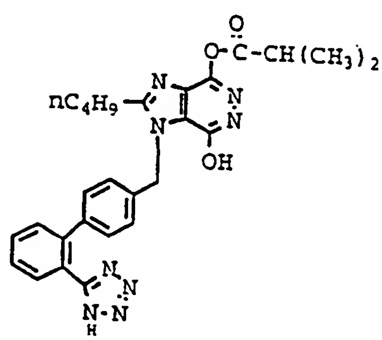
Compound #	Structure	Source
117		WO #91/19715 pub. 26 Dec 91
118		WO #91/19715 pub. 26 Dec 91
119		WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

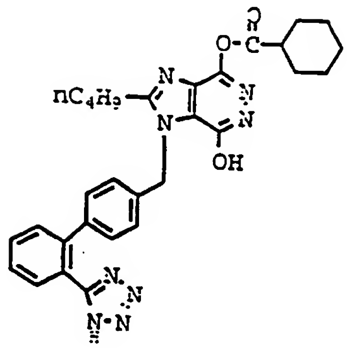
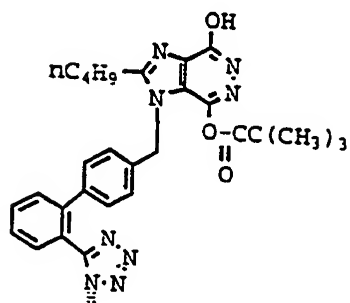
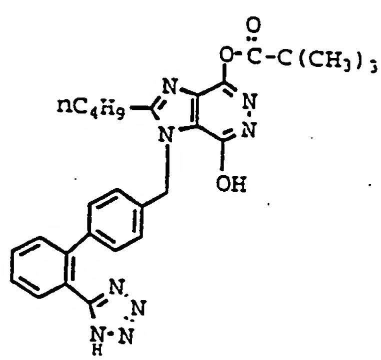
Compound #	Structure	Source
120		WO #91/19715 pub. 26 Dec 91
121		WO #91/19715 pub. 26 Dec 91
122		WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

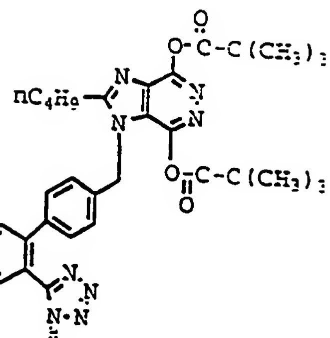
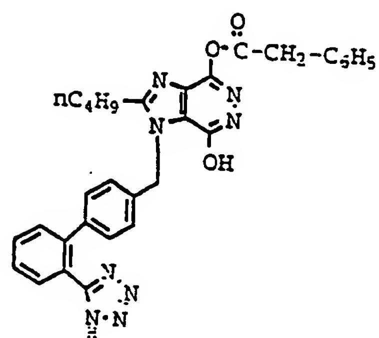
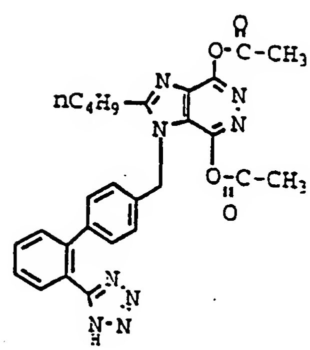
Compound #	Structure	Source
123		WO #91/19715 pub. 26 Dec 91
124		WO #91/19715 pub. 26 Dec 91
125		WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

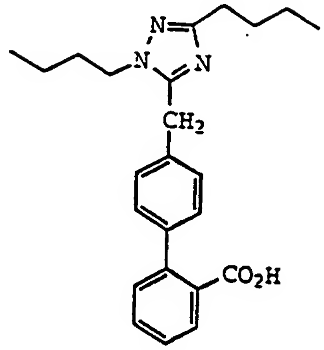
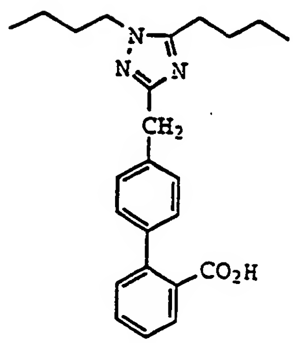
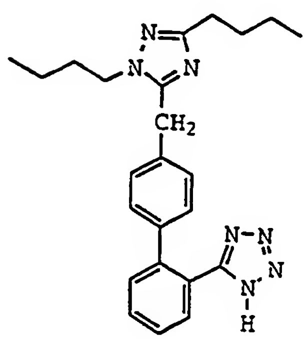
Compound #	Structure	Source
126		WO #92/05161 pub. 2 Apr 92
127		WO #92/05161 pub. 2 Apr 92
128		WO #92/05161 pub. 2 Apr 92

TABLE II: Angiotensin II Antagonists

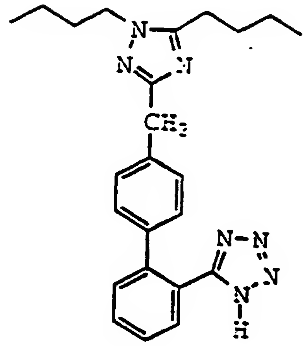
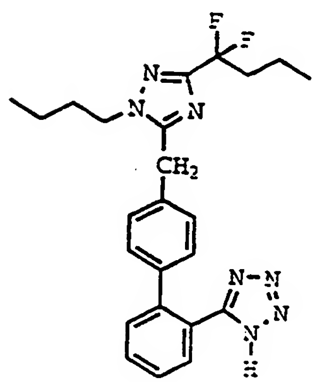
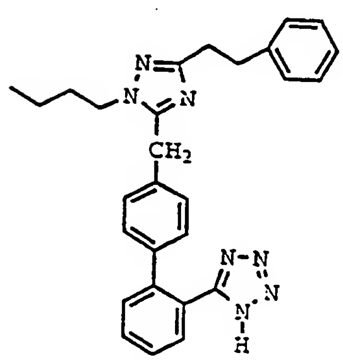
Compound #	Structure	Source
129		WO #92/05161 pub. 2 Apr 92
130		WO #92/05161 pub. 2 Apr 92
131		WO #92/05161 pub. 2 Apr 92

TABLE II: Angiotensin II Antagonists

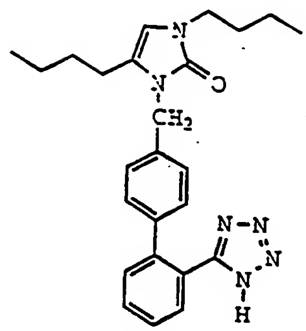
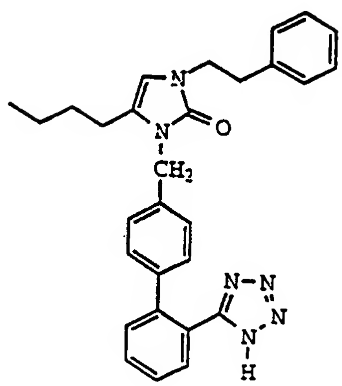
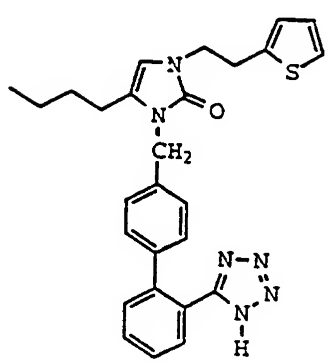
Compound #	Structure	Source
132		WO #92/07834 pub. 14 May 92
133		WO #92/07834 pub. 14 May 92
134		WO #92/07834 pub. 14 May 92

TABLE II: Angiotensin II Antagonists

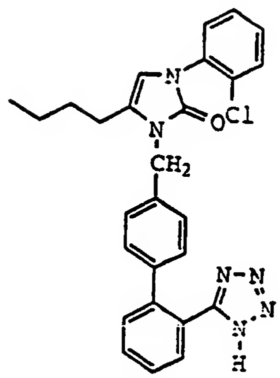
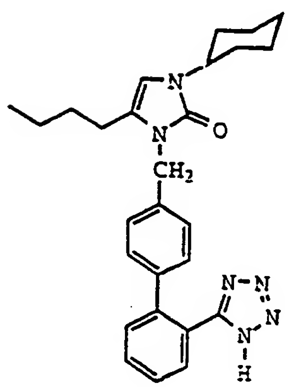
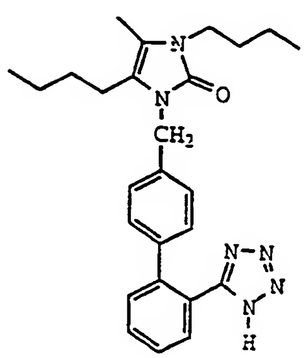
Compound #	Structure	Source
135		WO #92/07834 pub. 14 May 92
136		WO #92/07834 pub. 14 May 92
137		WO #92/07834 pub. 14 May 92

TABLE II: Angiotensin II Antagonists

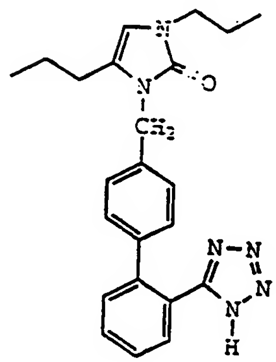
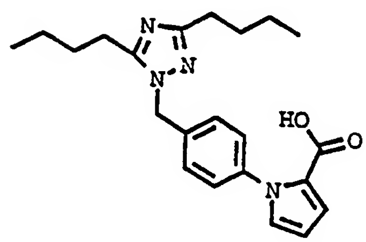
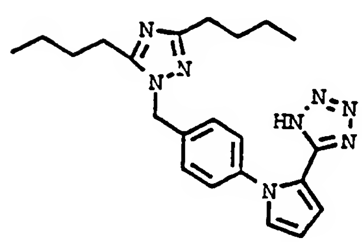
Compound #	Structure	Source
138		WO #92/07834 pub. 14 May 92
139		WO #92/11255 pub. 9 Jul 92
140		WO #92/11255 pub. 9 Jul 92

TABLE II: Angiotensin II Antagonists

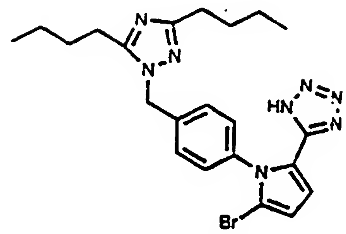
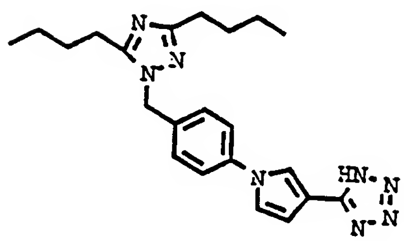
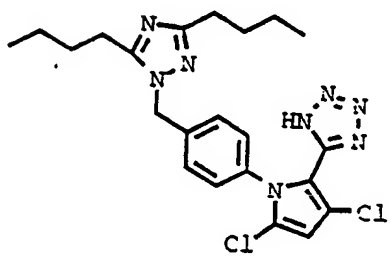
Compound #	Structure	Source
141		WO #92/11255 pub. 9 Jul 921
142		WO #92/11255 pub. 9 Jul 92
143		WO #92/11255 pub. 9 Jul 92

TABLE II: Angiotensin II Antagonists

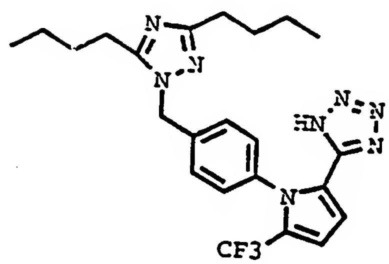
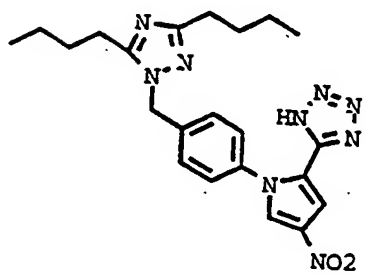
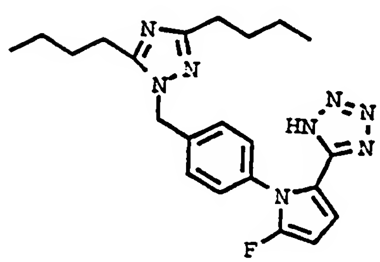
Compound #	Structure	Source
144		WO #92/11255 pub. 9 Jul 92
145		WO #92/11255 pub. 9 Jul 92
146		WO #92/11255 pub. 9 Jul 92

TABLE II: Angiotensin II Antagonists

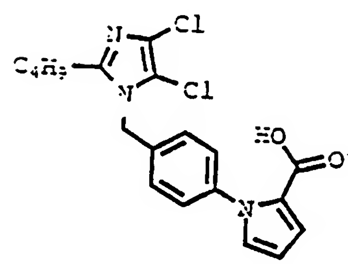
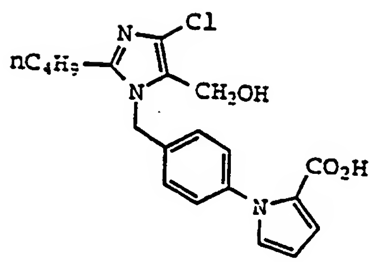
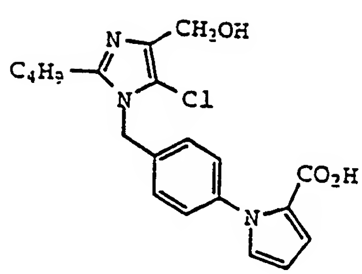
Compound #	Structure	Source
147		WO #92/15577 pub. 17 Sep 92
148		WO #92/15577 pub. 17 Sep 92
149		WO #92/15577 pub. 17 Sep 92

TABLE II: Angiotensin II Antagonists

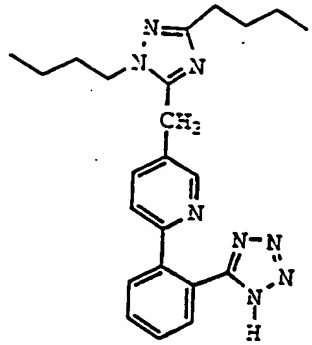
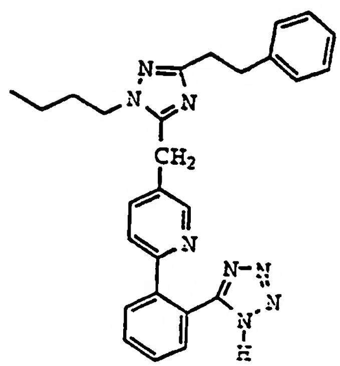
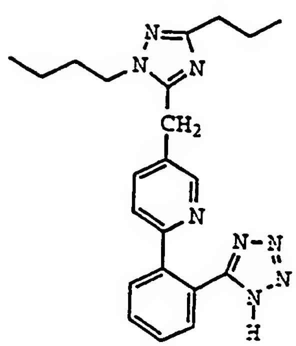
Compound #	Structure	Source
150		WO #92/16523 pub. 1 Oct 92
151		WO #92/16523 pub. 1 Oct 92
152		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

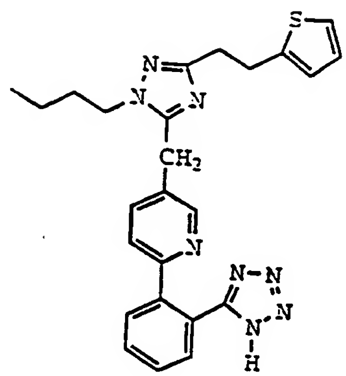
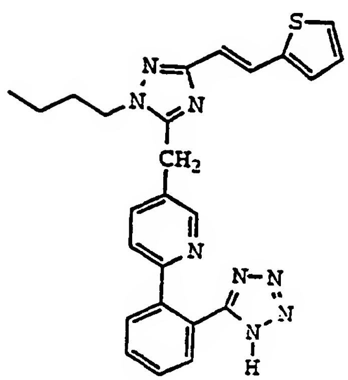
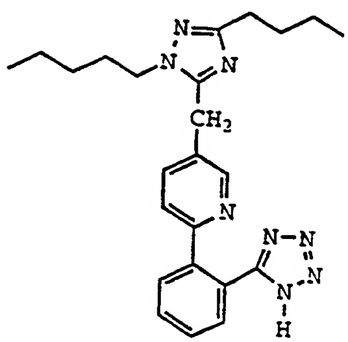
Compound #	Structure	Source
153		WO #92/16523 pub. 1 Oct 92
154		WO #92/16523 pub. 1 Oct 92
155		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

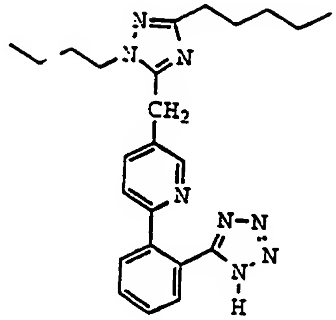
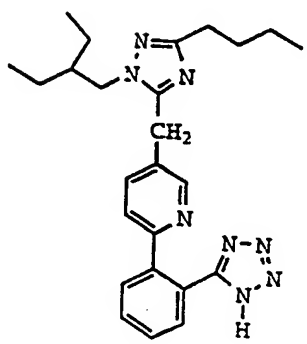
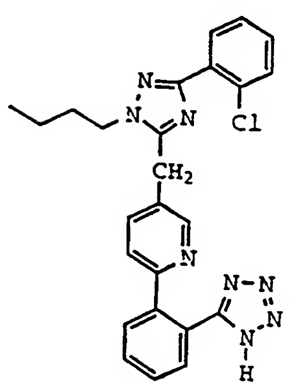
Compound #	Structure	Source
156		WO #92/16523 pub. 1 Oct 92
157		WO #92/16523 pub. 1 Oct 92
158		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

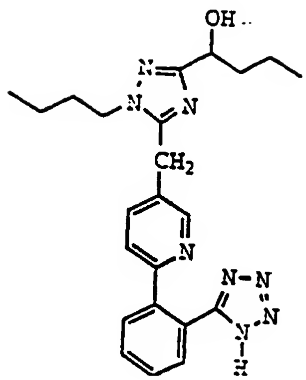
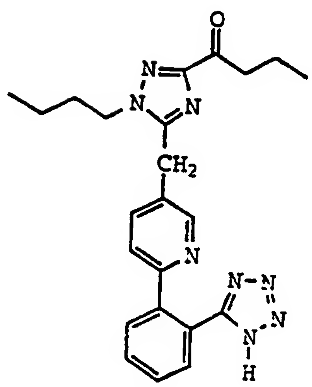
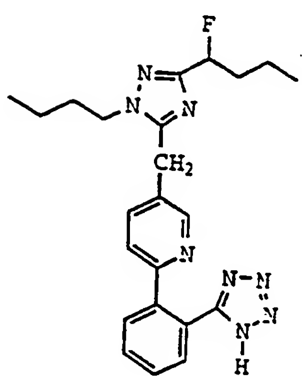
Compound #	Structure	Source
159		WO #92/16523 pub. 1 Oct 92
160		WO #92/16523 pub. 1 Oct 92
161		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

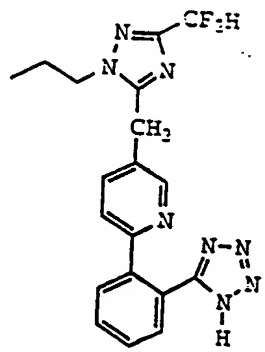
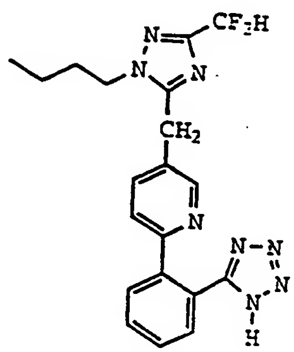
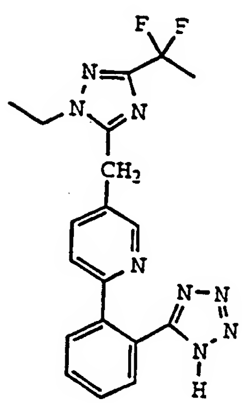
Compound #	Structure	Source
162		WO #92/16523 pub. 1 Oct 92
163		WO #92/16523 pub. 1 Oct 92
164		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

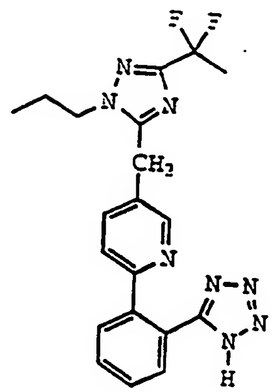
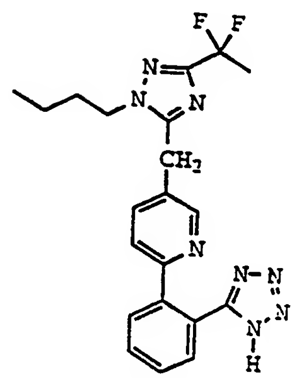
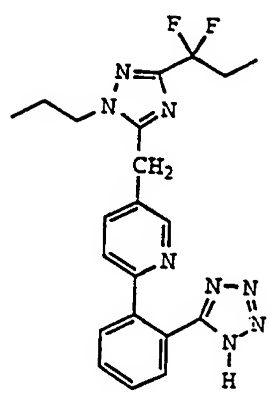
Compound #	Structure	Source
165		WO #92/16523 pub. 1 Oct 92
166		WO #92/16523 pub. 1 Oct 92
167		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

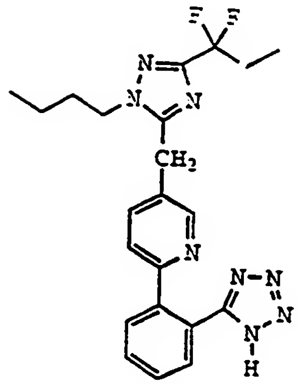
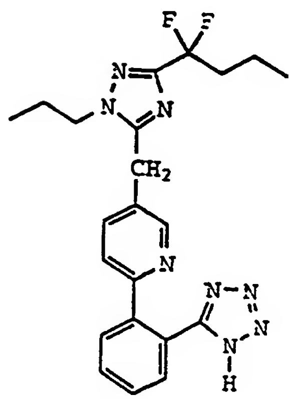
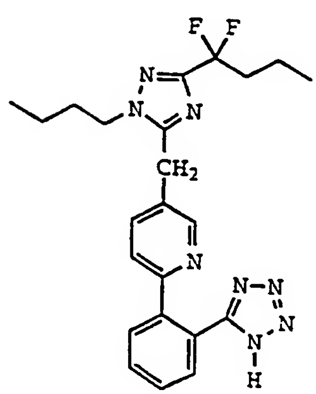
Compound #	Structure	Source
168		WO #92/16523 pub. 1 Oct 92
169		WO #92/16523 pub. 1 Oct 92
170		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

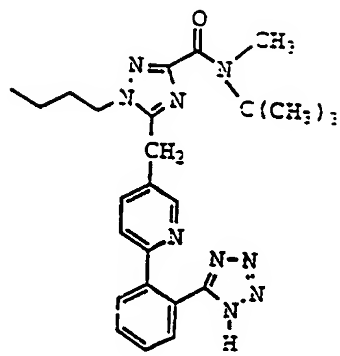
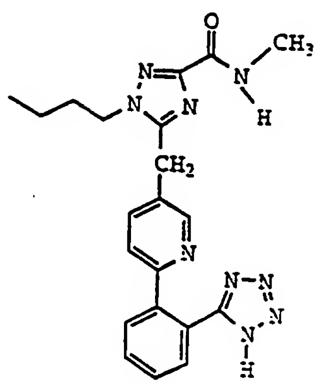
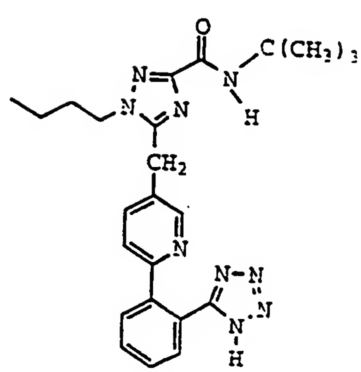
Compound #	Structure	Source
171		WO #92/16523 pub. 1 Oct 92
172		WO #92/16523 pub. 1 Oct 92
173		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

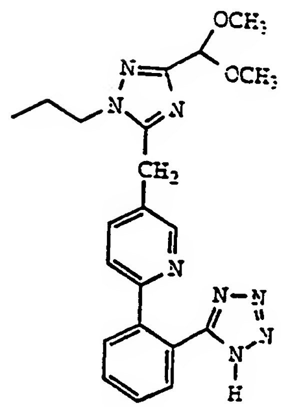
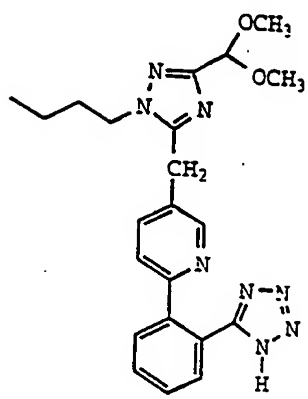
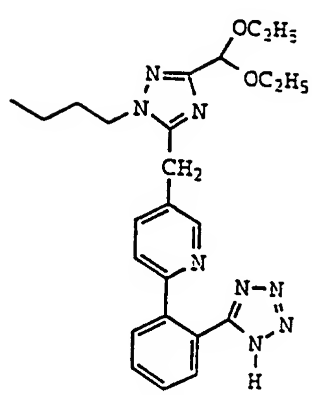
Compound #	Structure	Source
174		WO #92/16523 pub. 1 Oct 92
175		WO #92/16523 pub. 1 Oct 92
176		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

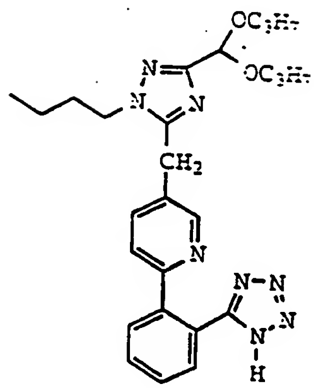
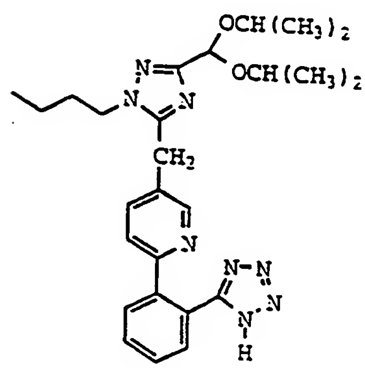
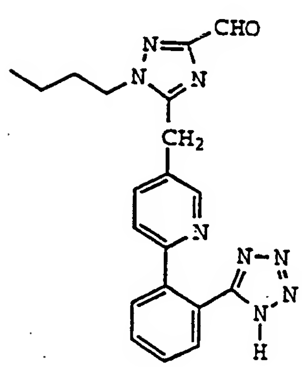
Compound #	Structure	Source
177		WO #92/16523 pub. 1 Oct 92
178		WO #92/16523 pub. 1 Oct 92
179		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

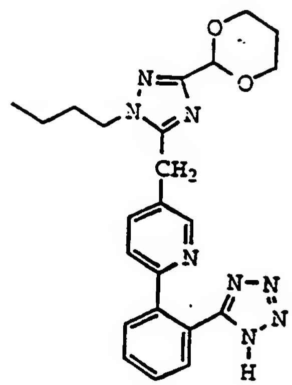
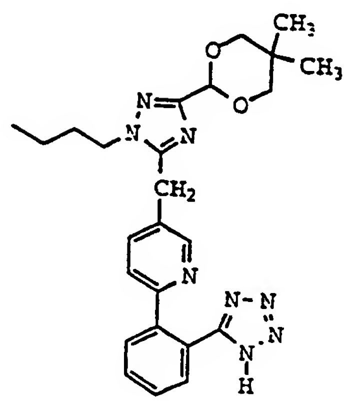
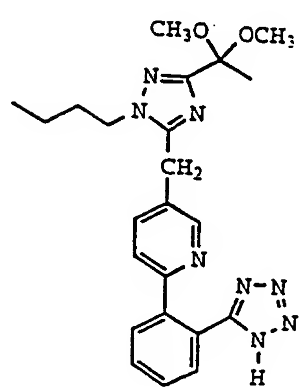
Compound #	Structure	Source
180		WO #92/16523 pub. 1 Oct 92
181		WO #92/16523 pub. 1 Oct 92
182		WO #92/16523 pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

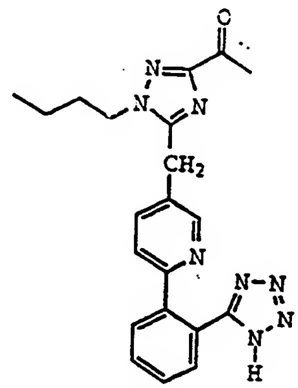
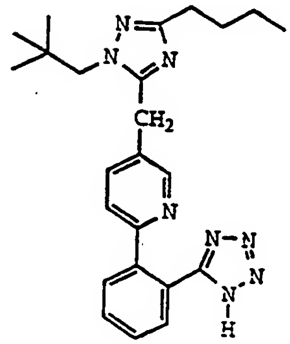
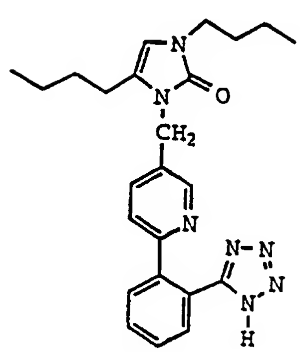
Compound #	Structure	Source
183		WO #92/16523 pub. 1 Oct 92
184		WO #92/16523 pub. 1 Oct 92
185		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

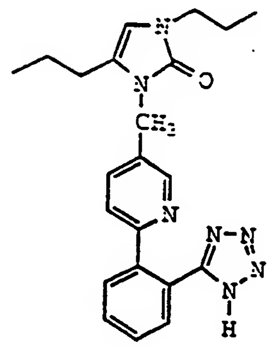
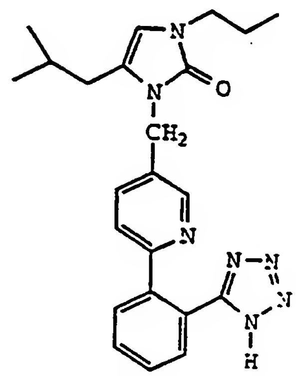
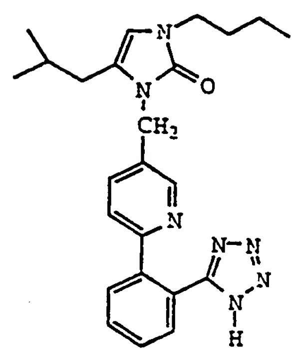
Compound #	Structure	Source
186		WO #92/17469 pub. 15 Oct 92
187		WO #92/17469 pub. 15 Oct 92
188		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

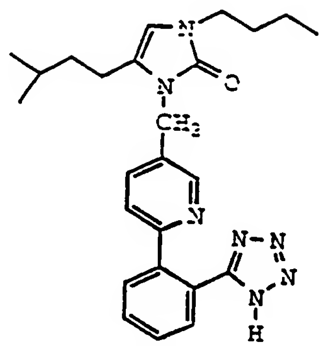
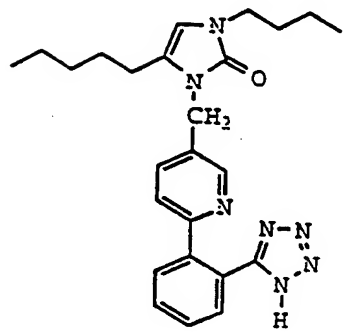
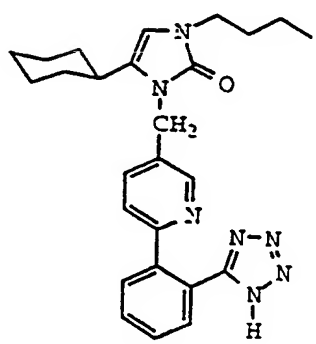
Compound #	Structure	Source
189		WO #92/17469 pub. 15 Oct 92
190		WO #92/17469 pub. 15 Oct 92
191		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

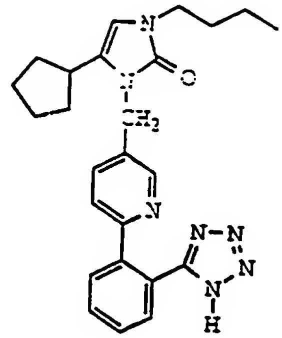
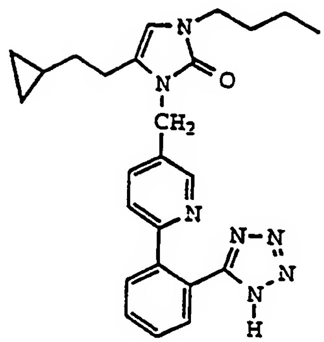
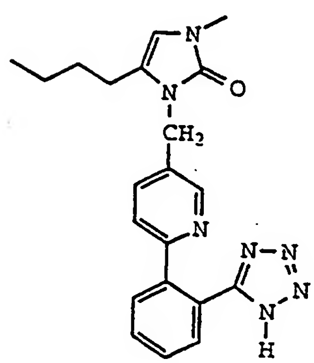
Compound #	Structure	Source
192		WO #92/17469 pub. 15 Oct 92
193		WO #92/17469 pub. 15 Oct 92
194		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

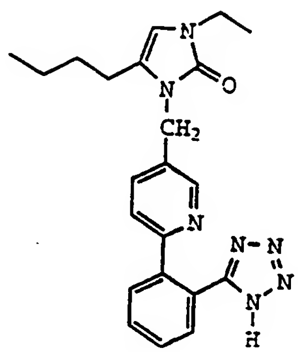
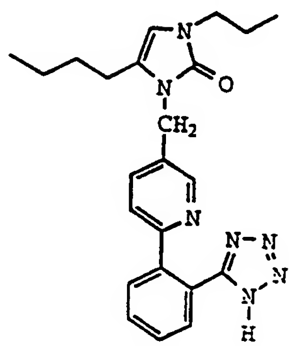
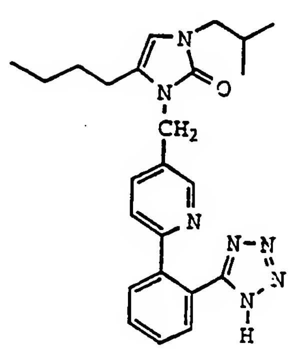
Compound #	Structure	Source
195		WO #92/17469 pub. 15 Oct 92
196		WO #92/17469 pub. 15 Oct 92
197		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

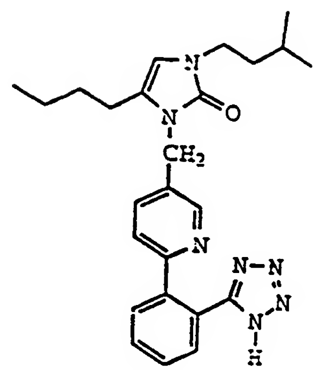
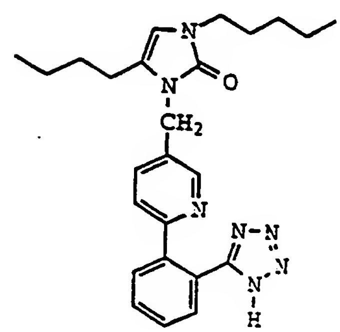
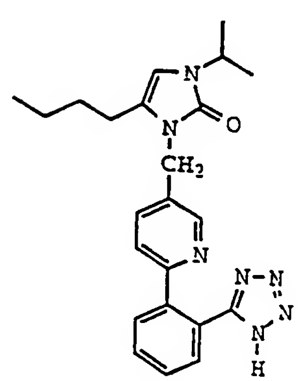
Compound #	Structure	Source
198		WO #92/17469 pub. 15 Oct 92
199		WO #92/17469 pub. 15 Oct 92
200		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

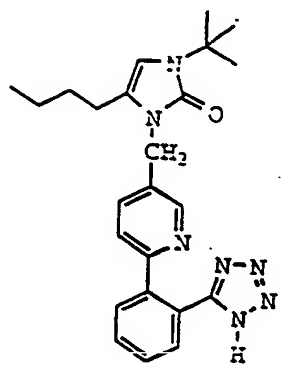
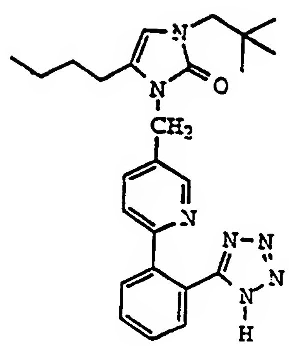
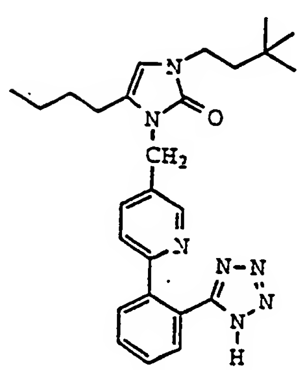
Compound #	Structure	Source
201		WO #92/17469 pub. 15 Oct 92
202		WO #92/17469 pub. 15 Oct 92
203		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

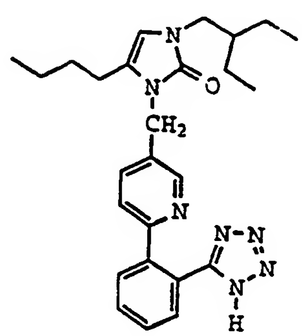
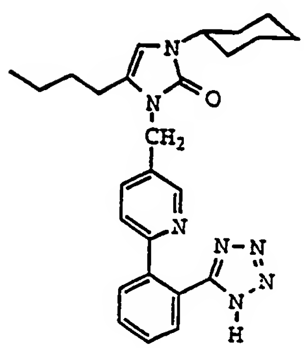
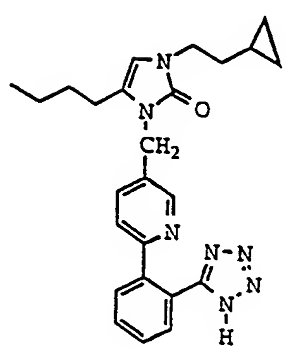
Compound #	Structure	Source
204		WO #92/17469 pub. 15 Oct 92
205		WO #92/17469 pub. 15 Oct 92
206		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

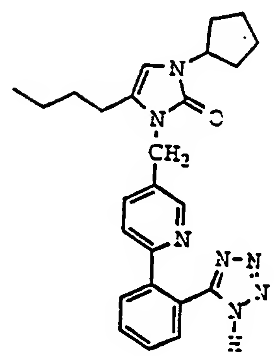
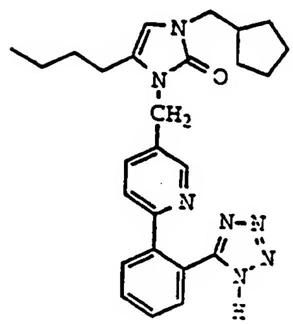
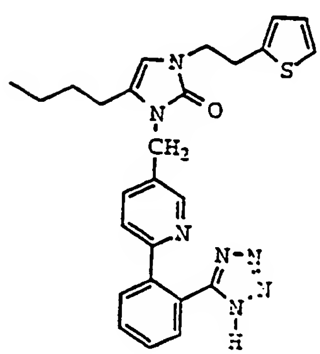
Compound #	Structure	Source
207		WO #92/17469 pub. 15 Oct 92
208		WO #92/17469 pub. 15 Oct 92
209		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

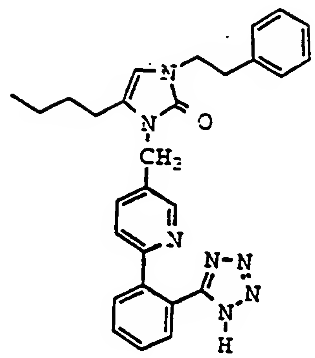
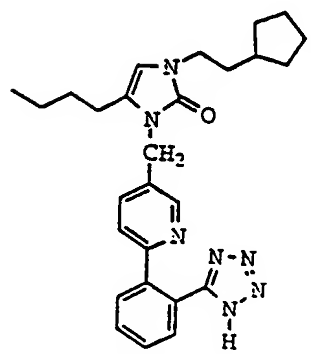
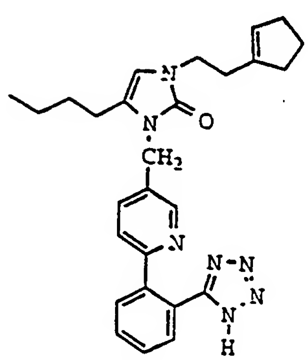
Compound #	Structure	Source
210		WO #92/17469 pub. 15 Oct 92
211		WO #92/17469 pub. 15 Oct 92
212		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

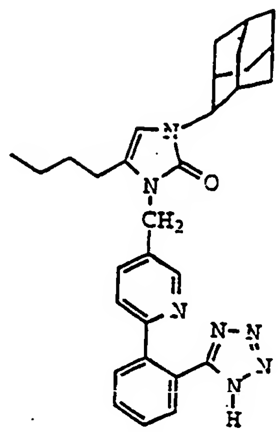
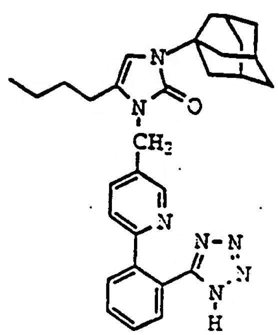
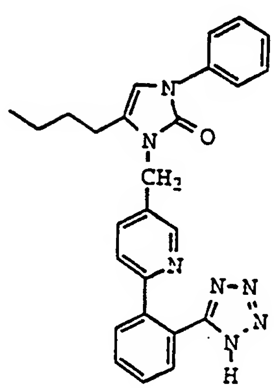
Compound #	Structure	Source
213		WO #92/17469 pub. 15 Oct 92
214		WO #92/17469 pub. 15 Oct 92
215		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

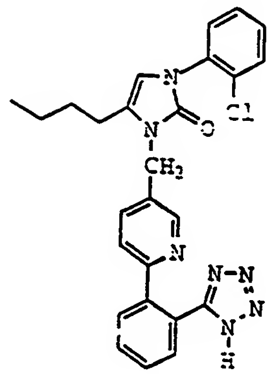
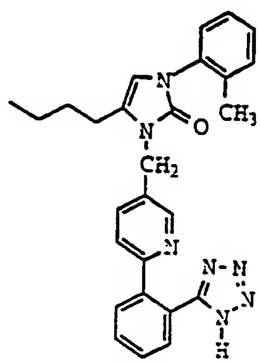
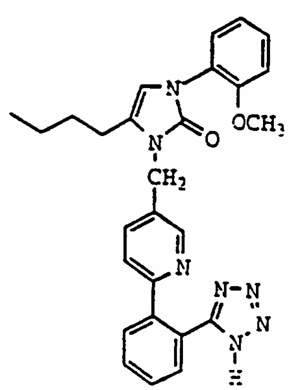
Compound #	Structure	Source
216		WO #92/17469 pub. 15 Oct 92
217		WO #92/17469 pub. 15 Oct 92
218		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

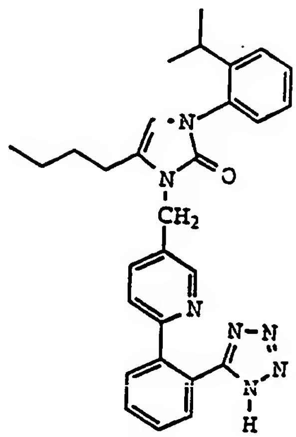
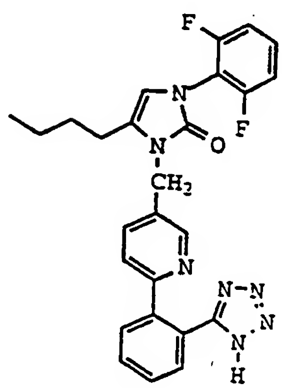
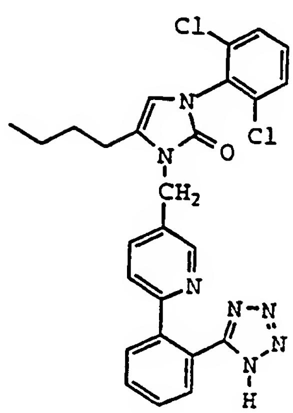
Compound #	Structure	Source
219		WO #92/17469 pub. 15 Oct 92
220		WO #92/17469 pub. 15 Oct 92
221		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

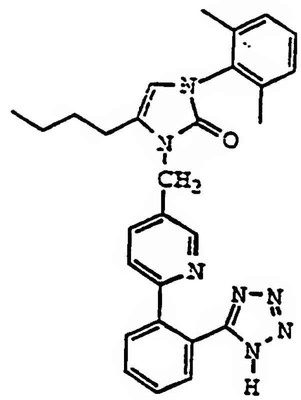
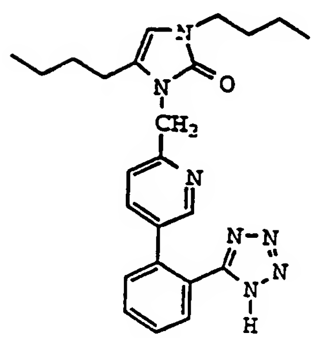
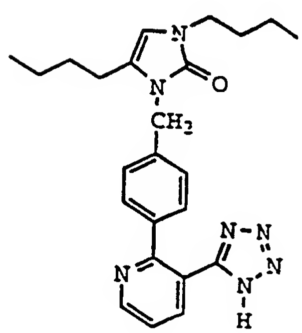
Compound #	Structure	Source
222		WO #92/17469 pub. 15 Oct 92
223		WO #92/17469 pub. 15 Oct 92
224		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

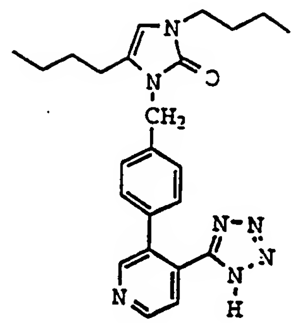
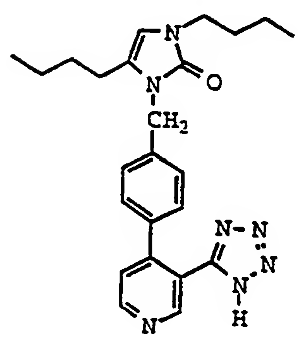
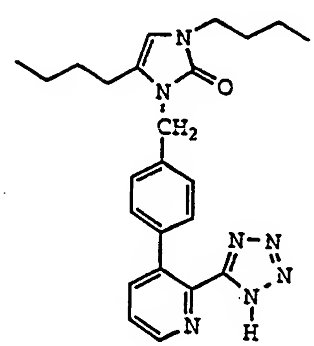
Compound #	Structure	Source
225		WO #92/17469 pub. 15 Oct 92
226		WO #92/17469 pub. 15 Oct 92
227		WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

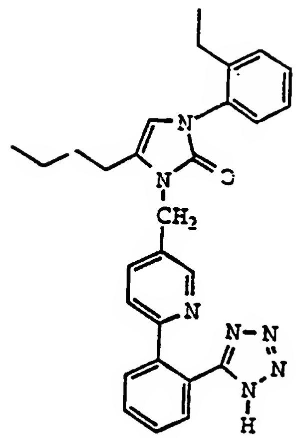
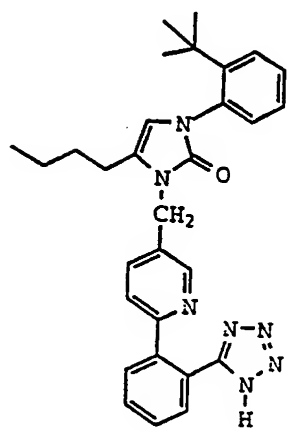
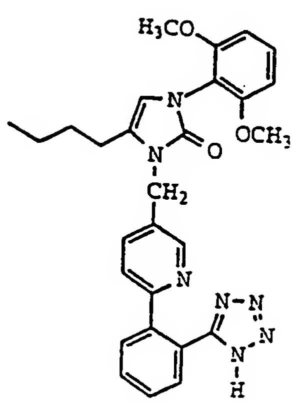
Compound #	Structure	Source
228		
229		
230		

TABLE II: Angiotensin II Antagonists

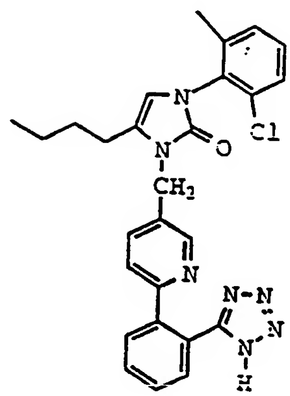
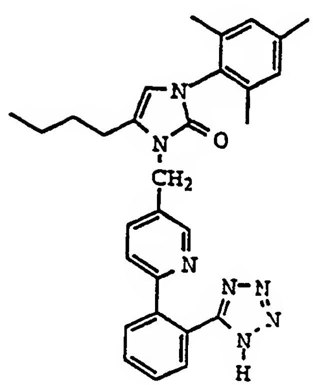
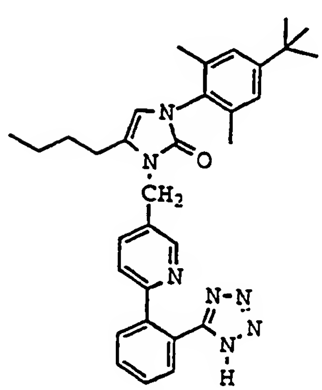
Compound #	Structure	Source
231		
232		
233		

TABLE II: Angiotensin II Antagonists

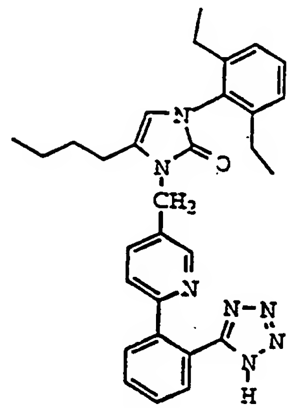
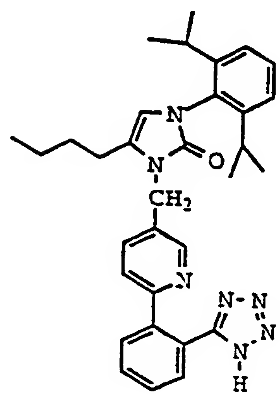
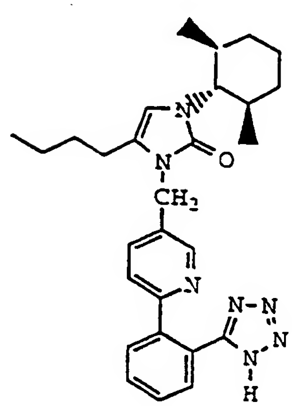
Compound #	Structure	Source
234		
235		
236		

TABLE II: Angiotensin II Antagonists

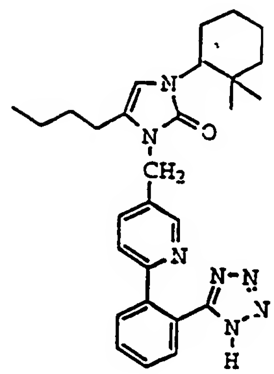
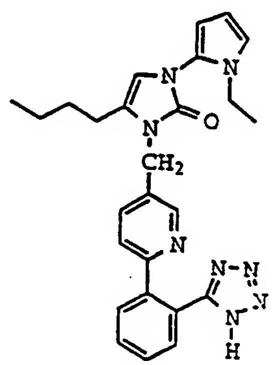
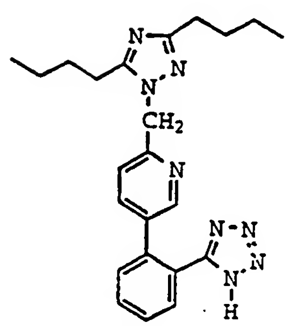
Compound #	Structure	Source
237		
238		
239		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

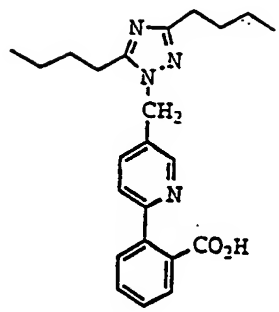
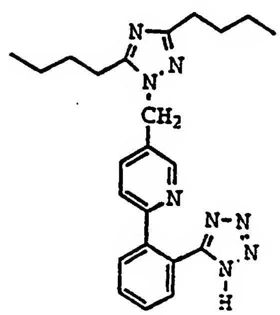
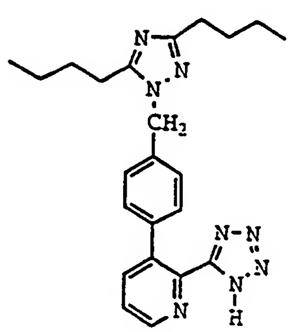
Compound #	Structure	Source
240		WO #92/18092 pub. 29 Oct 92
241		WO #92/18092 pub. 29 Oct 92
242		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

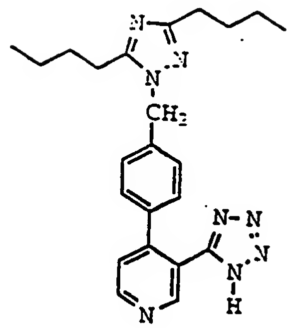
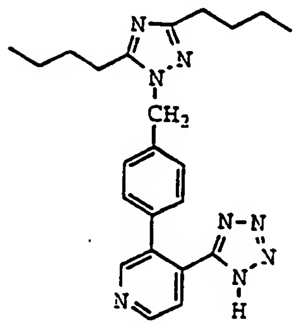
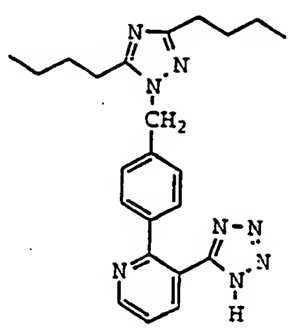
Compound #	Structure	Source
243		WO #92/18092 pub. 29 Oct 92
244		WO #92/18092 pub. 29 Oct 92
245		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

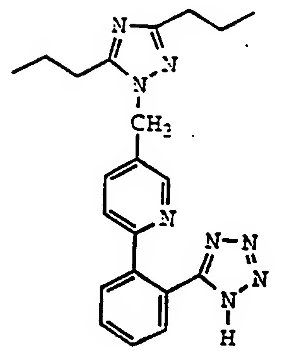
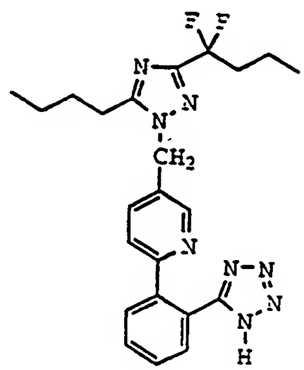
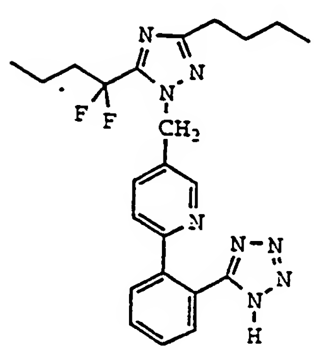
Compound #	Structure	Source
246		WO #92/18092 pub. 29 Oct 92
247		WO #92/18092 pub. 29 Oct 92
248		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

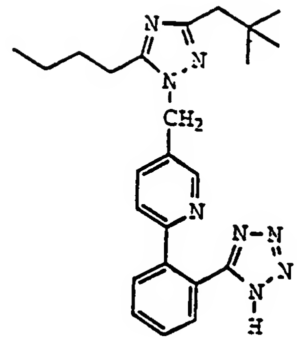
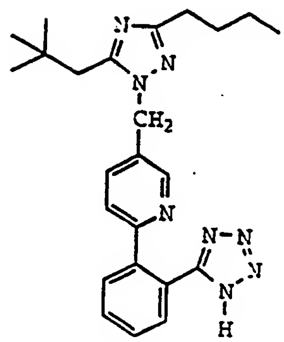
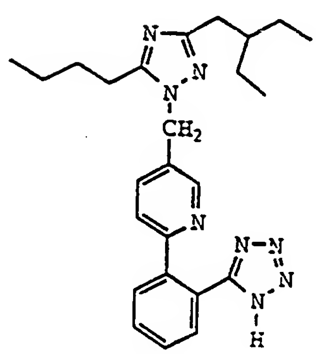
Compound #	Structure	Source
249		WO #92/18092 pub. 29 Oct 92
250		WO #92/18092 pub. 29 Oct 92
251		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

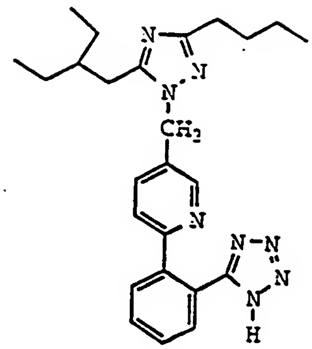
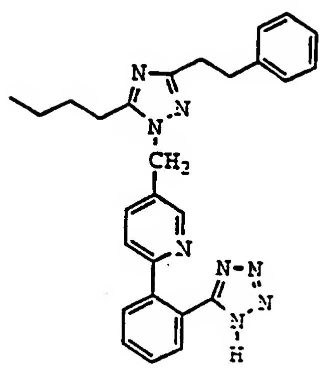
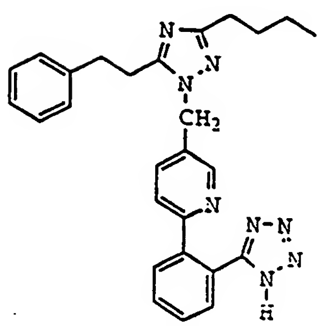
Compound #	Structure	Source
252		WO #92/18092 pub. 29 Oct 92
253		WO #92/18092 pub. 29 Oct 92
254		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

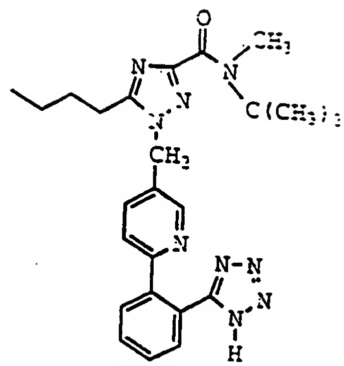
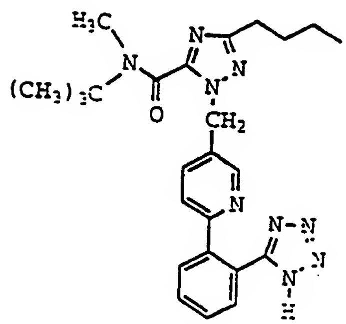
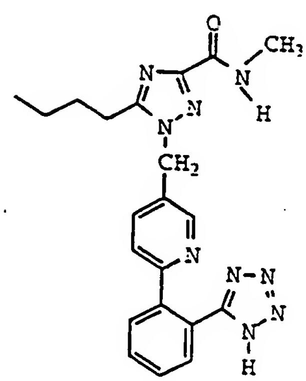
Compound #	Structure	Source
255		WO #92/18092 pub. 29 Oct 92
256		WO #92/18092 pub. 29 Oct 92
257		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

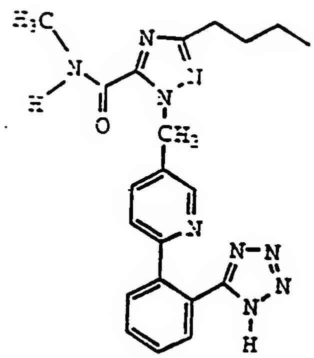
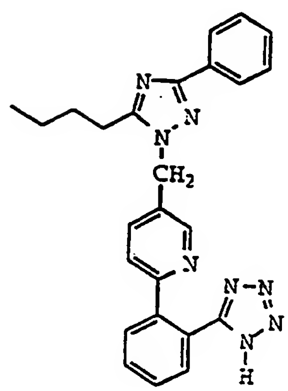
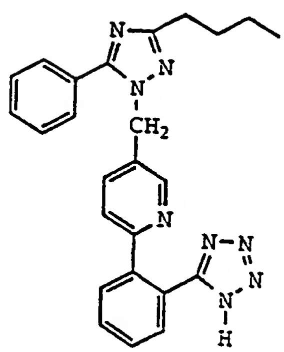
Compound #	Structure	Source
258		WO #92/18092 pub. 29 Oct 92
259		WO #92/18092 pub. 29 Oct 92
260		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

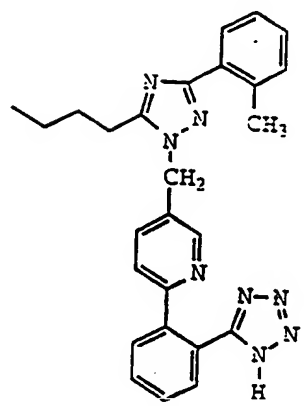
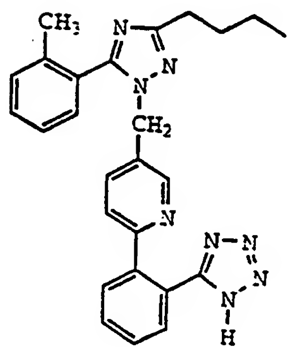
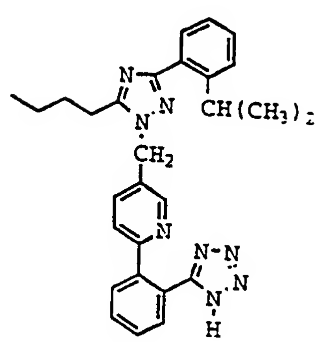
Compound #	Structure	Source
261		WO #92/18092 pub. 29 Oct 92
262		WO #92/18092 pub. 29 Oct 92
263		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

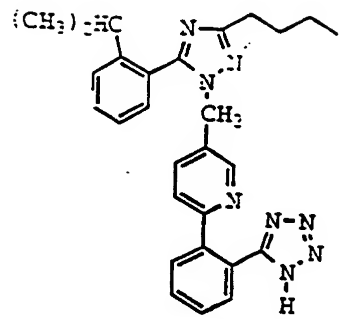
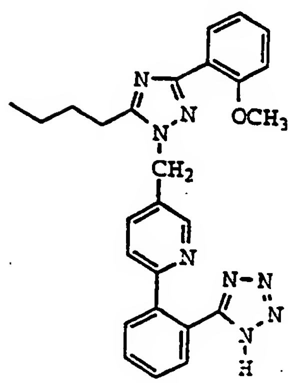
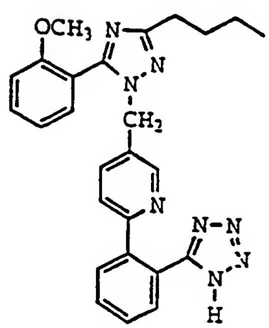
Compound #	Structure	Source
264		WO #92/18092 pub. 29 Oct 92
265		WO #92/18092 pub. 29 Oct 92
266		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

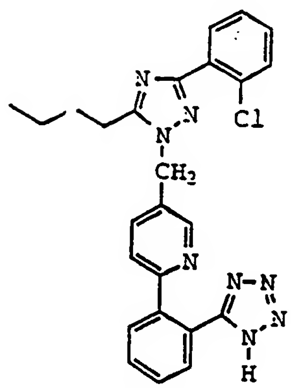
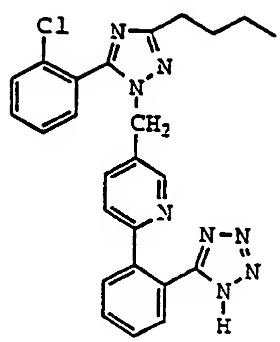
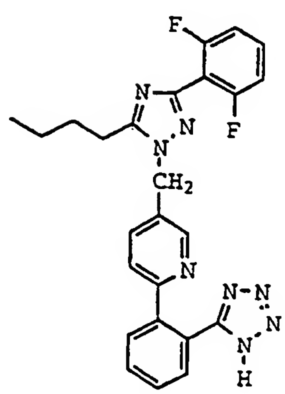
Compound #	Structure	Source
267		WO #92/18092 pub. 29 Oct 92
268		WO #92/18092 pub. 29 Oct 92
269		WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

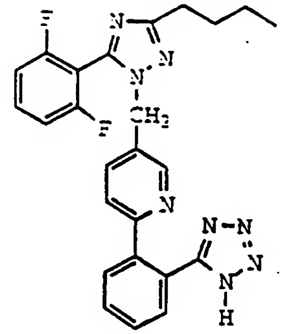
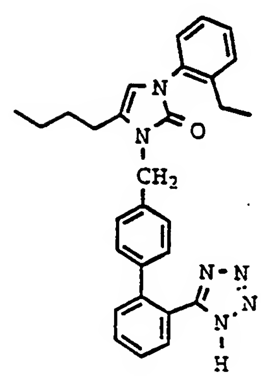
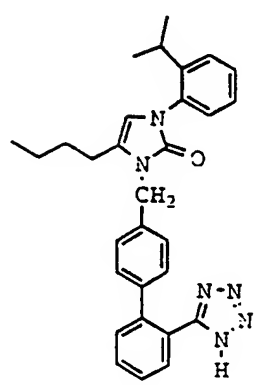
Compound #	Structure	Source
270		WO #92/18092 pub. 29 Oct 92
271		PCT/US95/02156 filed 8 Mar 94
272		PCT/US94/02156 filed 8 Mar 94

TABLE II: Angiotensin II Antagonists

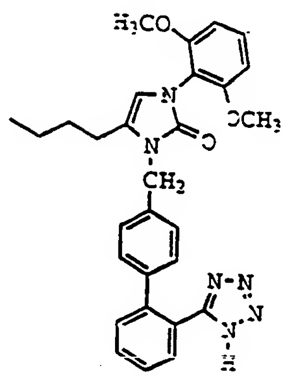
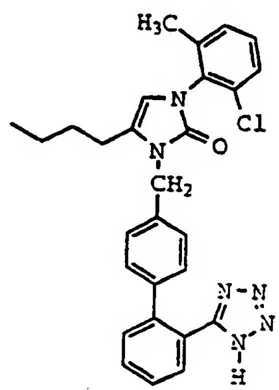
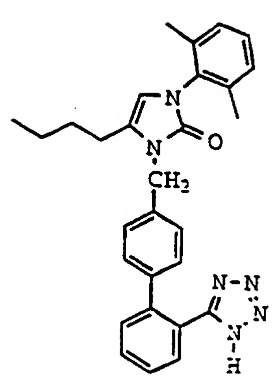
Compound #	Structure	Source
273		PCT/US94/02156 filed 8 Mar 94
274		PCT/US94/02156 filed 8 Mar 94
275		PCT/US94/02156 filed 8 Mar 94

TABLE II: Angiotensin II Antagonists

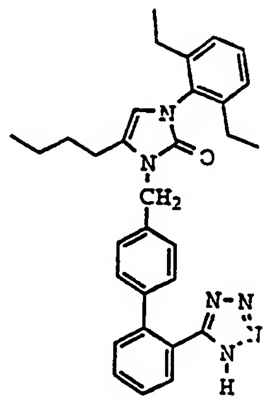
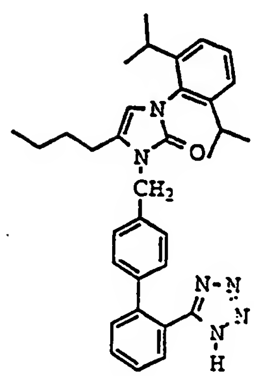
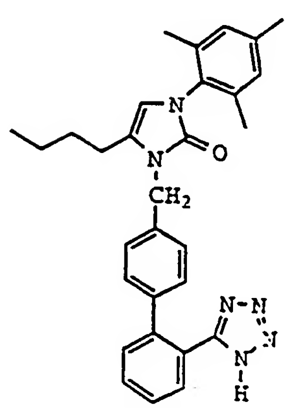
Compound #	Structure	Source
276		PCT/US94/02156 filed 8 Mar 94
277		PCT/US94/02156 filed 8 Mar 94
278		PCT/US94/02156 filed 8 Mar 94

TABLE II: Angiotensin II Antagonists

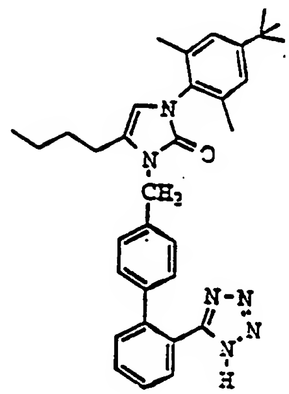
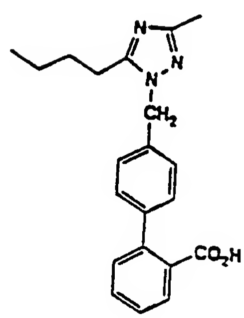
Compound #	Structure	Source
279		PCT/US94/02156 filed 8 Mar. 94
280		WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

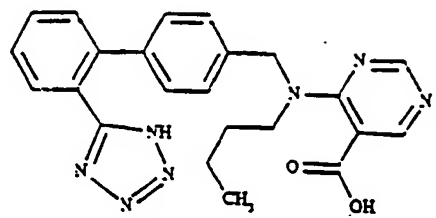
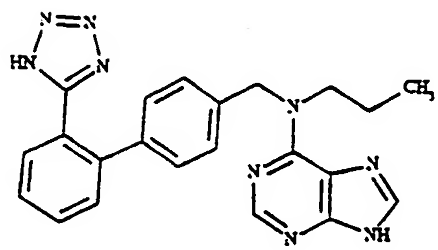
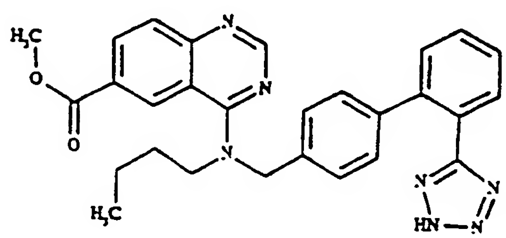
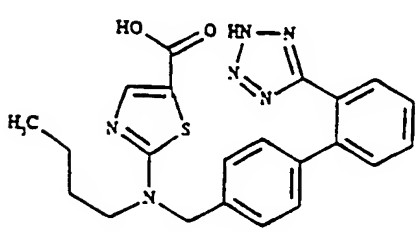
Compound #	Structure	Source
281		EP #475,206 pub. 18 Mar 92
282		WO #93/18035 pub. 16 Sep 93
283		WO #93/17628 pub. 16 Sep 93
284		WO #93/17681 pub. 16 Sep 93

TABLE II: Angiotensin II Antagonists

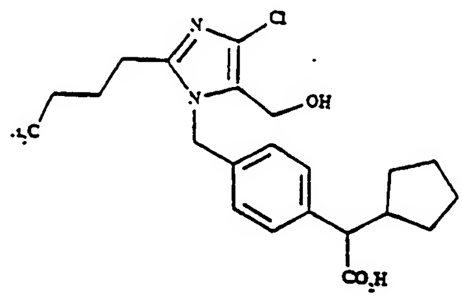
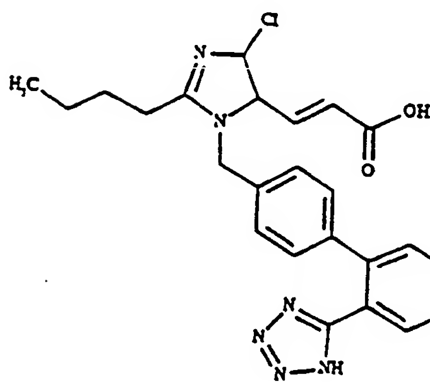
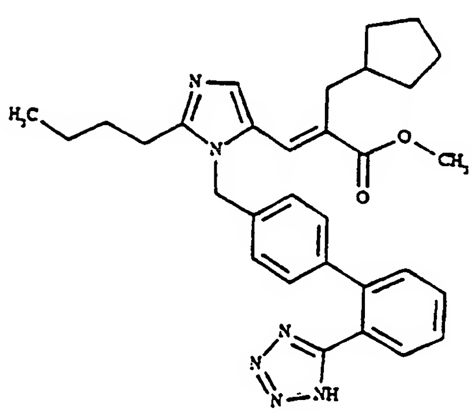
Compound #	Structure	Source
285		EP #513,533 pub. 19 Nov 92
286		EP #535,463 pub. 07 Apr 93
287		EP #535,465 pub. 07 Apr 93

TABLE II: Angiotensin II Antagonists

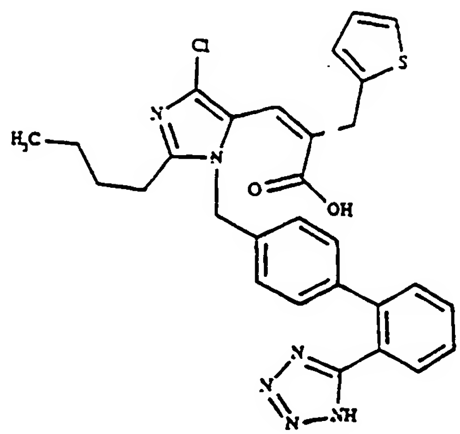
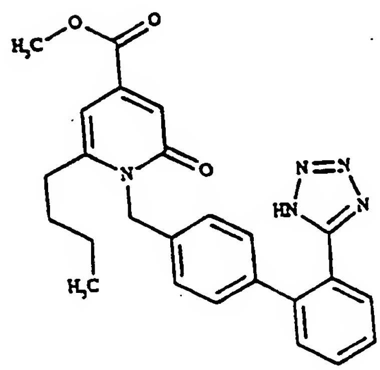
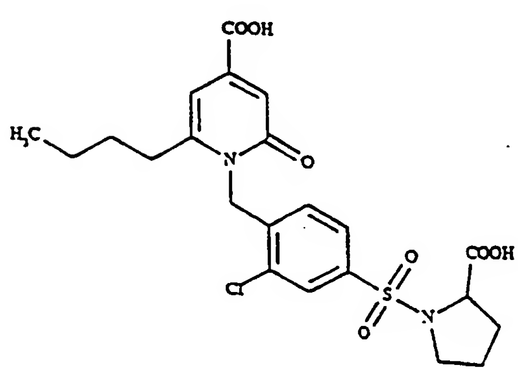
Compound #	Structure	Source
288		EP #539,713 pub. 05 May 93
289		EP #542,059 pub. 19 May 93
290		EP #05 557,843 pub. 01 Sep 93

TABLE II: Angiotensin II Antagonists

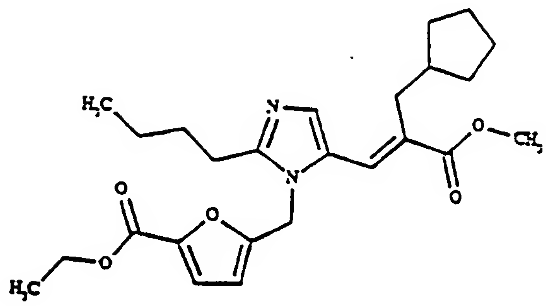
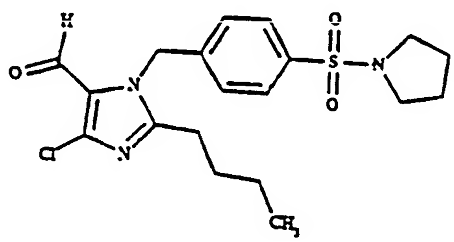
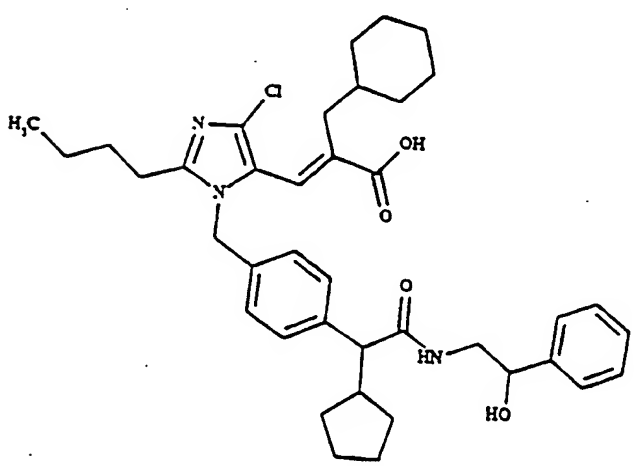
Compound #	Structure	Source
291		EP #563,705 pub. 06 Oct 93
292		EP #562,261 pub. 29 Sep 93
293		EP #05 557,843 pub. 15 Sep 93

TABLE II: Angiotensin II Antagonists

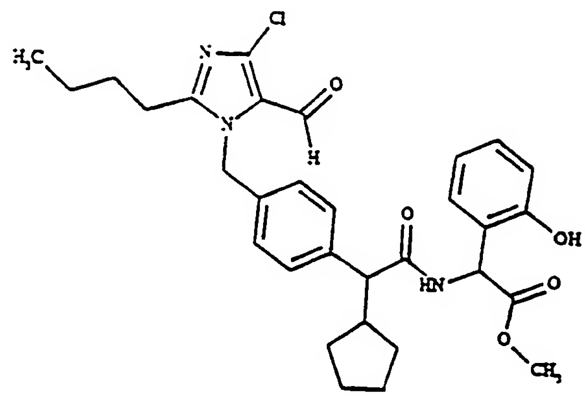
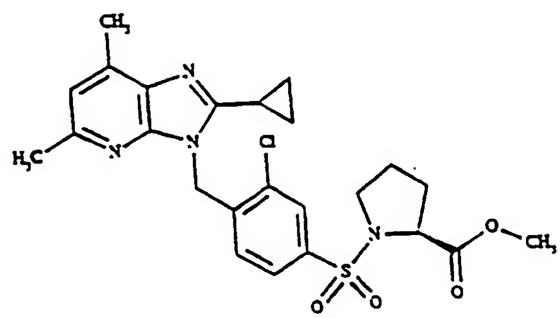
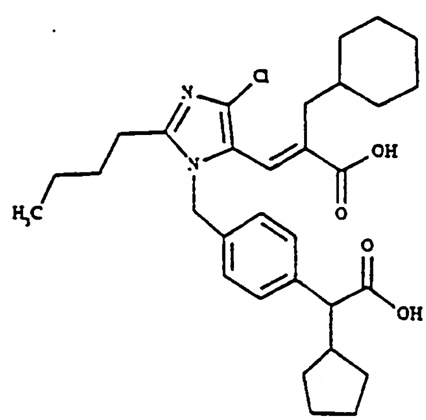
Compound #	Structure	Source
294		EP #560,163 pub. 15 Sep 93
295		EP #564, 788 pub. 13 Oct 93
296		EP #565,986 pub. 20 Oct 93

TABLE II: Angiotensin II Antagonists

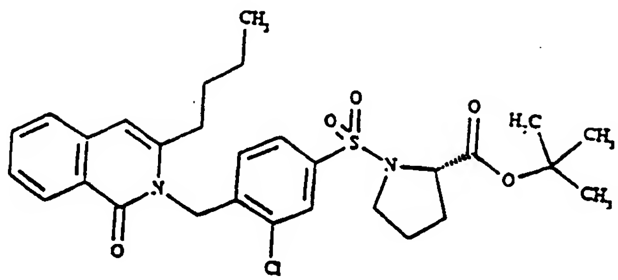
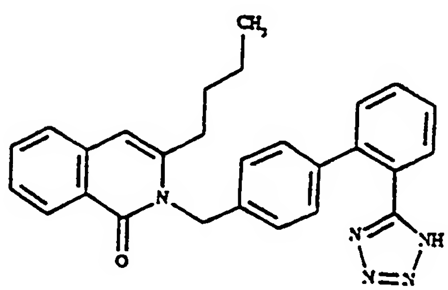
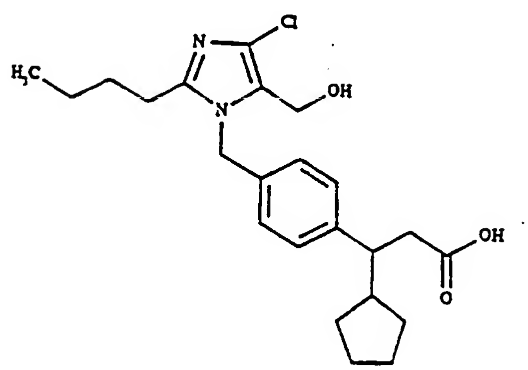
Compound #	Structure	Source
297		EP #0,569,795 pub. 18 Nov 93
298		EP #0,569,794 pub. 18 Nov 93
299		EP #0,578,002 pub. 12 Jan 94

TABLE II: Angiotensin II Antagonists

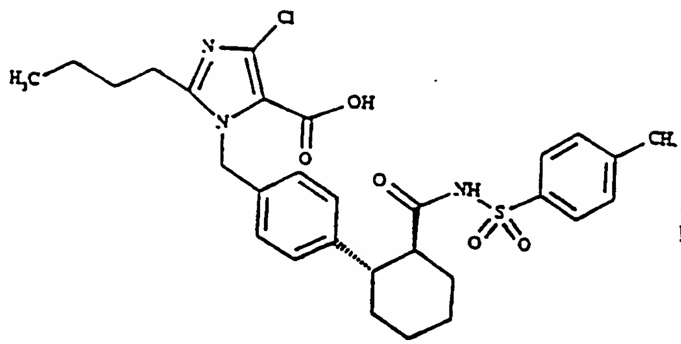
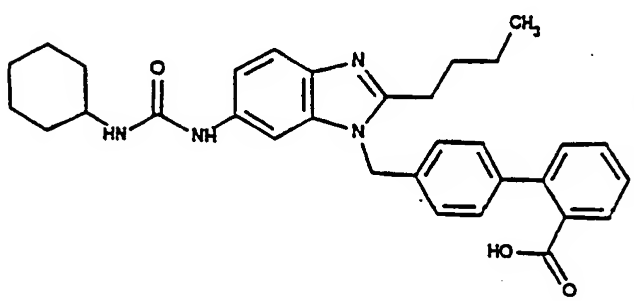
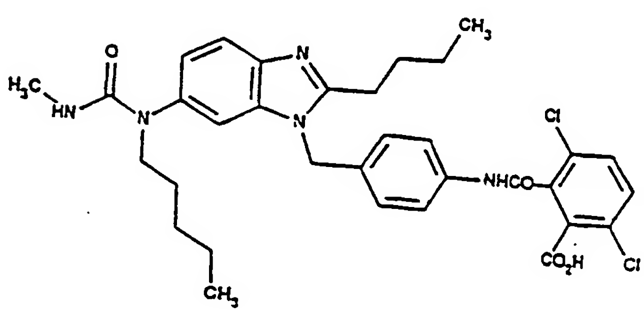
Compound #	Structure	Source
300		EP #581,003 pub. 02 Feb 94
301		EP #392,317 pub. 17 Oct 90
302		EP #392,317 pub. 17 Oct 90

TABLE II: Angiotensin II Antagonists

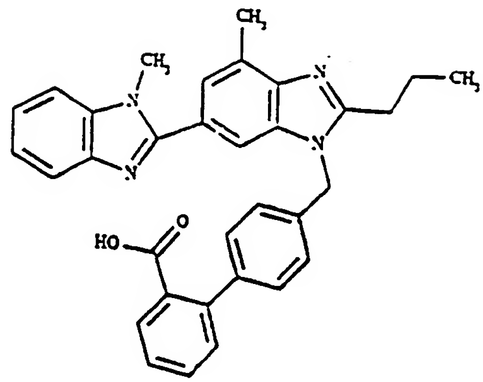
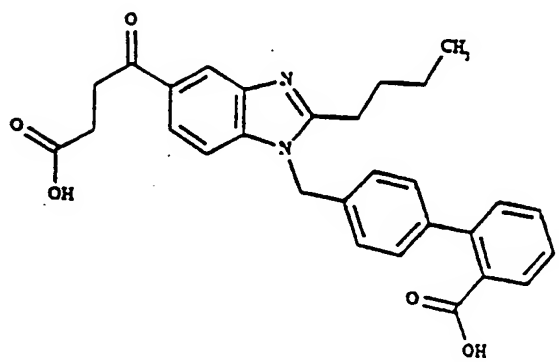
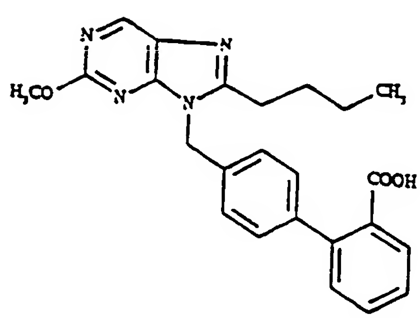
Compound #	Structure	Source
303		EP #502,314 pub. 09 Sep 92
304		EP #468,740 pub. 29 Jan 92
305		EP #470,543 pub. 12 Feb 92

TABLE II: Angiotensin II Antagonists

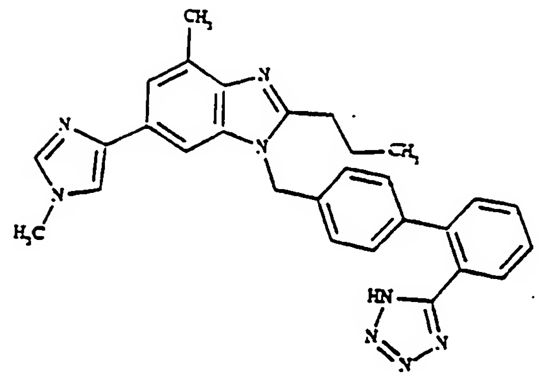
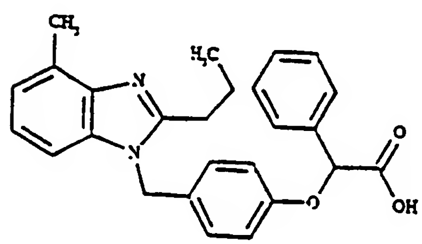
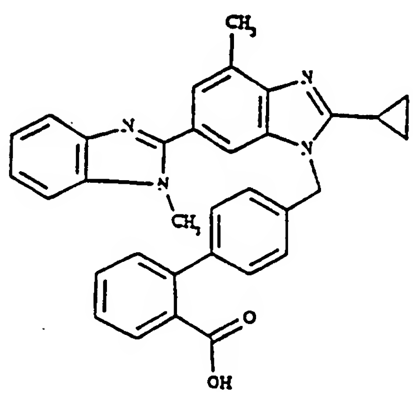
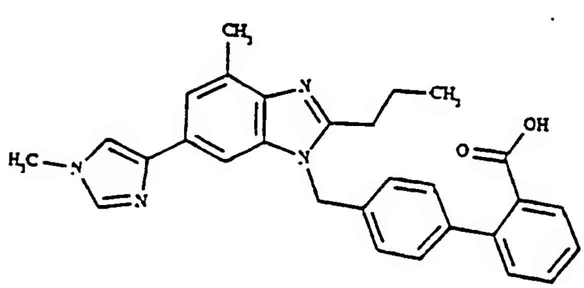
Compound #	Structure	Source
306		EP #502,314 pub. 09 Sep 92
307		EP #529,253 pub. 03 Mar 93
308		EP #543,263 pub. 26 May 93
309		EP #552,765 pub. 28 Jul 93

TABLE II: Angiotensin II Antagonists

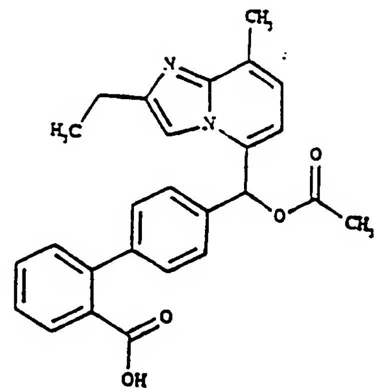
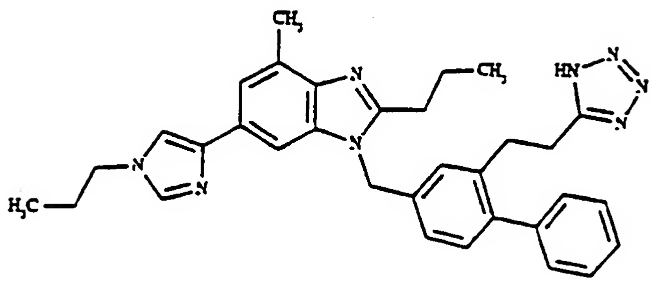
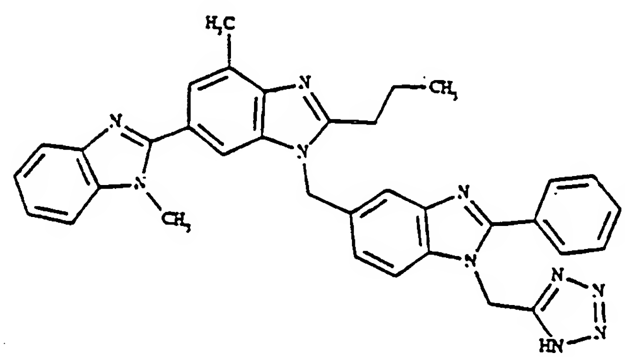
Compound #	Structure	Source
310		EP #555,825 pub. 18 Aug 93
311		EP #556,789 pub. 25 Aug 93
312		EP #560,330 pub. 15 Sep 93

TABLE II: Angiotensin II Antagonists

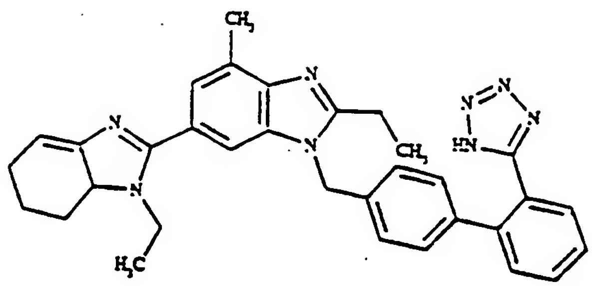
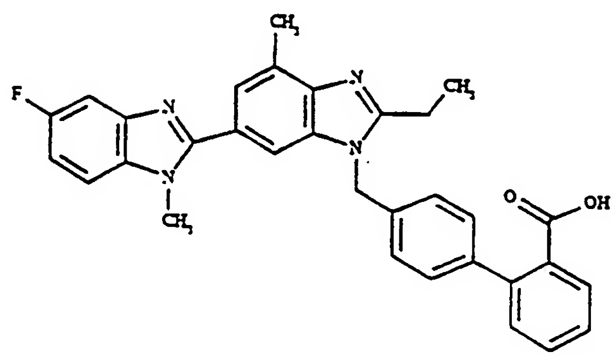
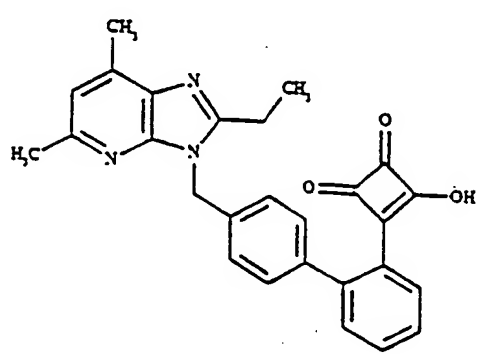
Compound #	Structure	Source
313		EP #566,020 pub. 20 Oct 93
314		EP #581,166 pub. 02 Feb 94
315		WO #94/01436 pub. 20 Jan 94

TABLE II: Angiotensin II Antagonists

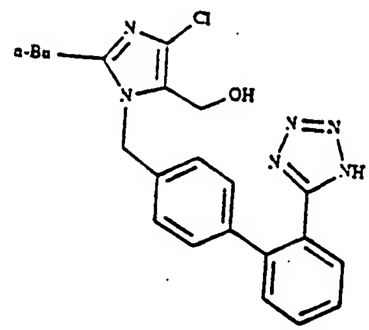
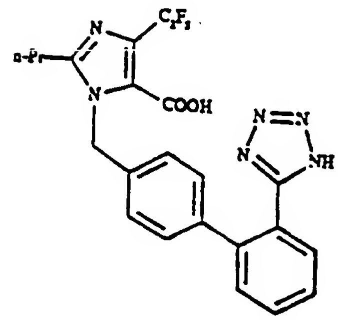
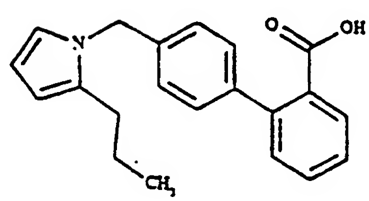
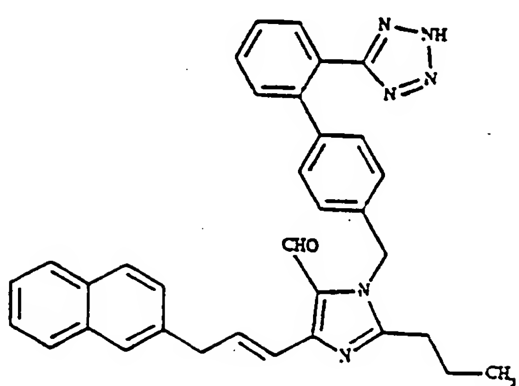
Compound #	Structure	Source
316		EP #253,310 pub. 20 Jan 88
317		EP #324,377 pub. 19 Jul 89
318		US #5,043,349 issued 27 Aug 91
319		WO #91/00281 pub. 10 Jan 91

TABLE II: Angiotensin II Antagonists

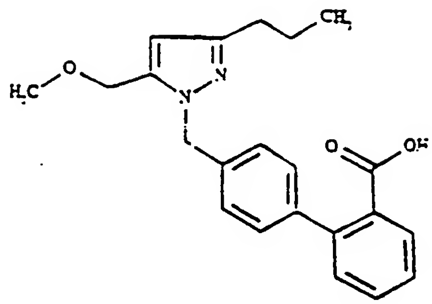
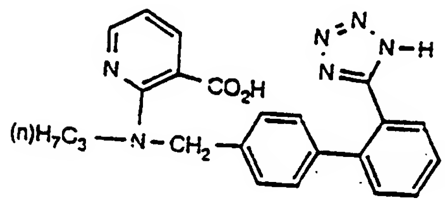
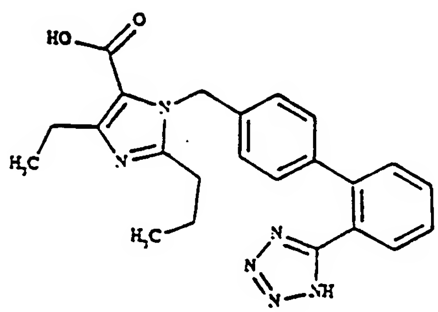
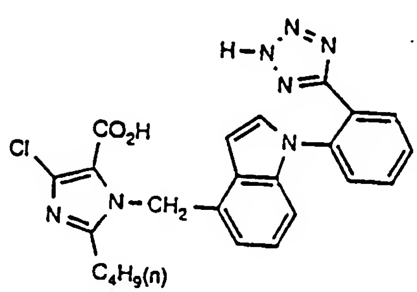
Compound #	Structure	Source
320		US #5,015,651 pub. 14 May 91
321		
322		WO #92/00977 pub. 23 Jan 92
323		

TABLE II: Angiotensin II Antagonists

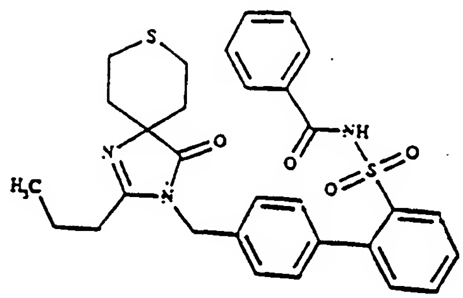
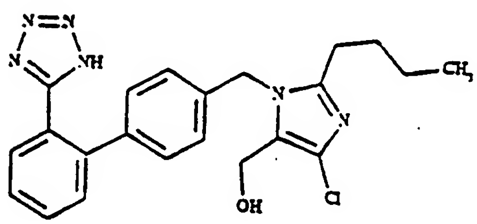
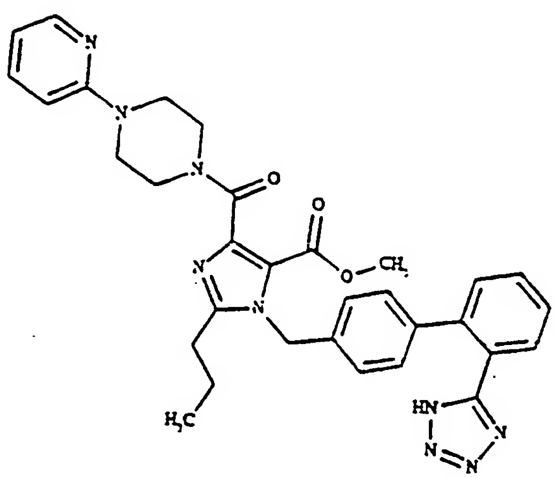
Compound #	Structure	Source
324		WO #93/04046 pub. 04 Mar 93
325		WO #93/10106 pub. 27 May 93
326		US #5,219,856 pub. 15 Jun 93

TABLE II: Angiotensin II Antagonists

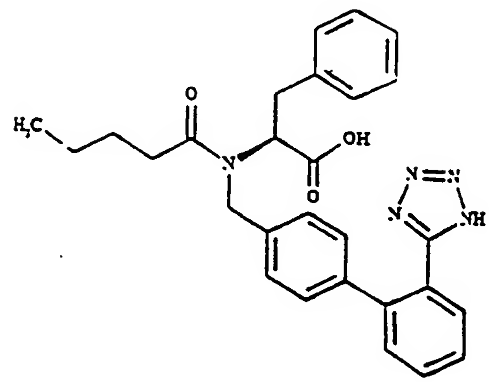
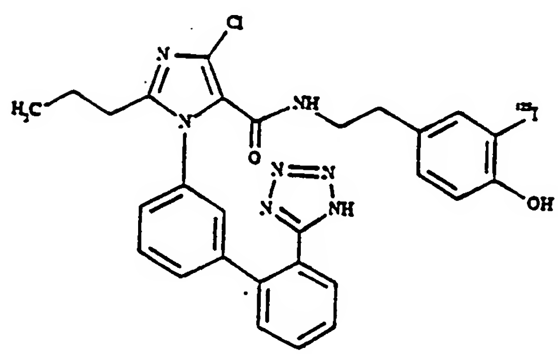
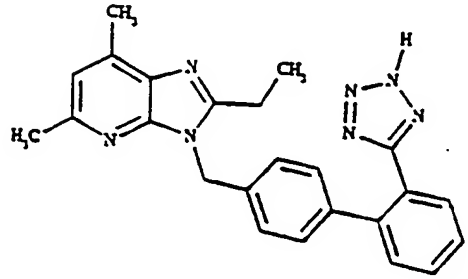
Compound #	Structure	Source
327		US #5,260,325 pub. 09 Nov 93
328		US #5,264,581 pub. 23 Nov 93
329		EP #400,974 pub. 05 Dec 90

TABLE II: Angiotensin II Antagonists

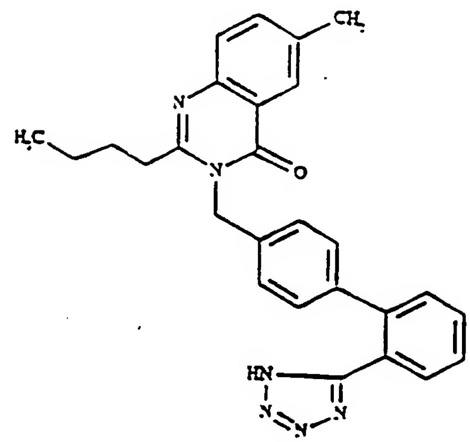
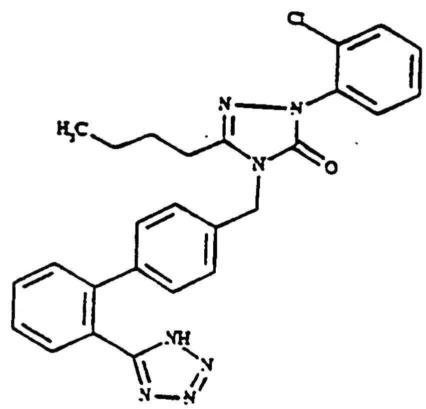
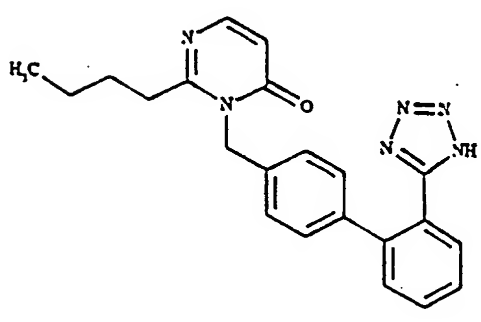
Compound #	Structure	Source
330		EP #411,766 pub. 06 Feb 91
331		EP #412,594 pub. 13 Feb 91
332		EP #419,048 pub. 27 Mar 91

TABLE II: Angiotensin II Antagonists

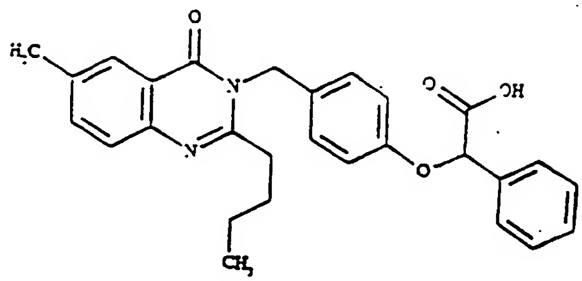
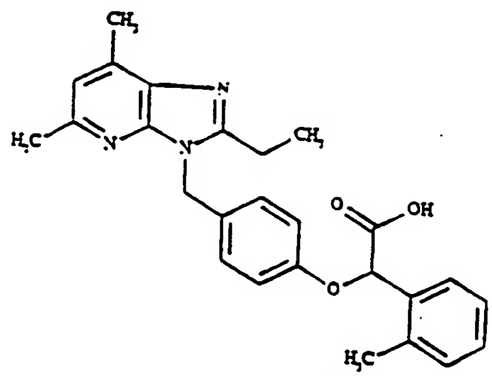
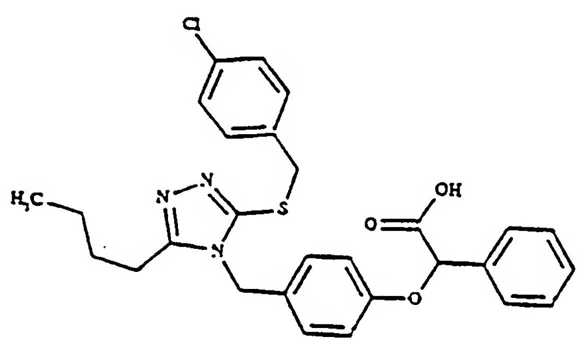
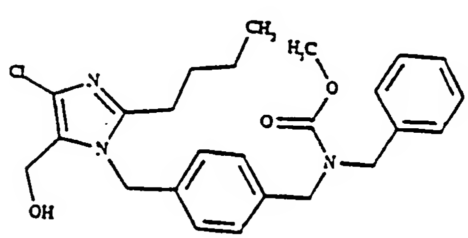
Compound #	Structure	Source
333		WO #91/12,001 pub. 22 Aug 91
334		WO #91/11,999 pub. 22 Aug 91
335		WO #91/11,909 pub. 22 Aug 91
336		WO #91/12,002 pub. 22 Aug 91

TABLE II: Angiotensin II Antagonists

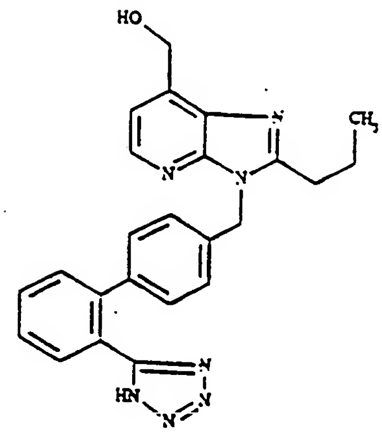
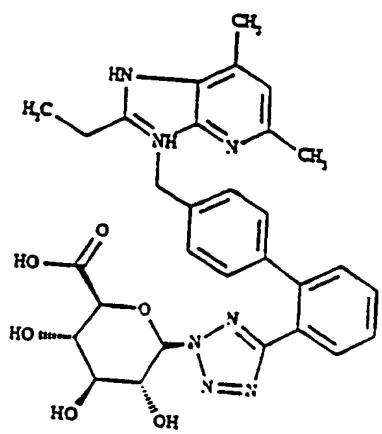
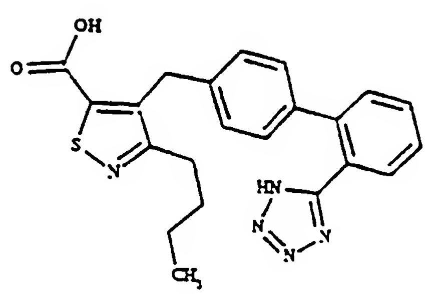
Compound #	Structure	Source
337		US #5,053,329 pub. 01 Oct 91
338		US #5,057,522 pub 15 Oct 91
339		WO #91/15,479 pub. 17 Oct 91

TABLE II: Angiotensin II Antagonists

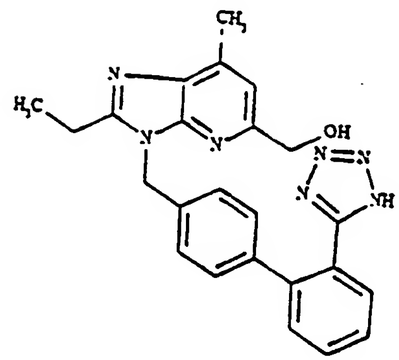
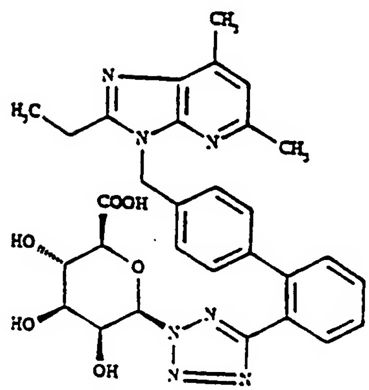
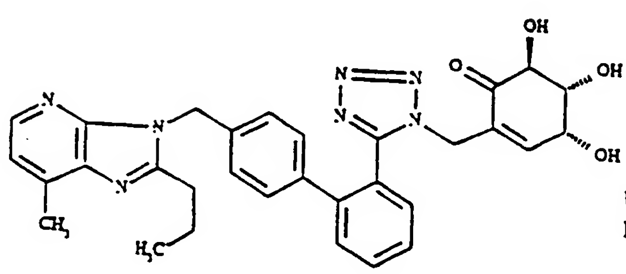
Compound #	Structure	Source
340		EP #456,510 pub. 13 Nov 91
341		EP #467,715 pub. 22 Jan 92
342		US #5,087,702 pub. 11 Feb 92

TABLE II: Angiotensin II Antagonists

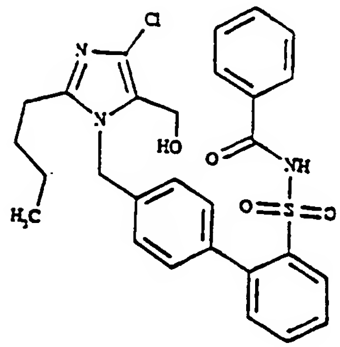
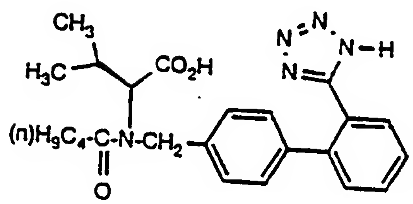
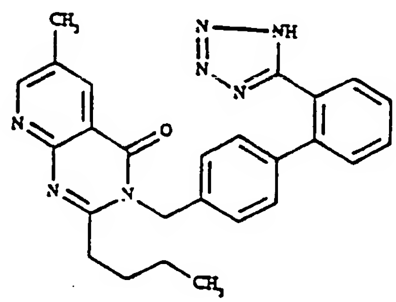
Compound #	Structure	Source
343		EP #479,479 pub. 08 Apr 92
344		
345		EP #481,614 pub. 22 Apr 92

TABLE II: Angiotensin II Antagonists

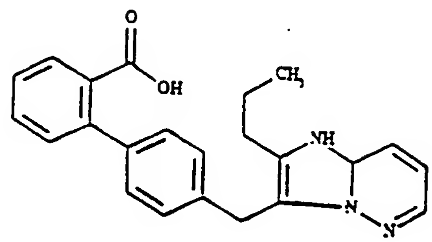
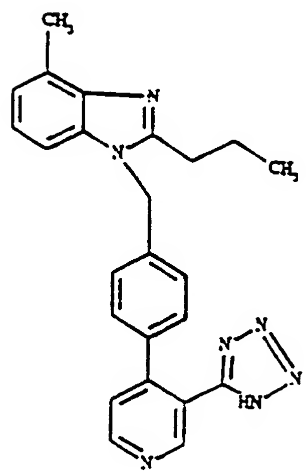
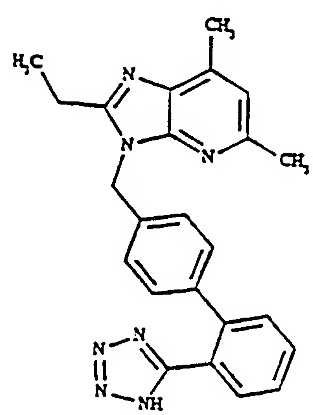
Compound #	Structure	Source
346		EP #490,587 pub. 17 Jun 92
347		US #5,128,327 pub. 07 Jul 92
348		US #5,132,216 pub. 21 Jul 92

TABLE II: Angiotensin II Antagonists

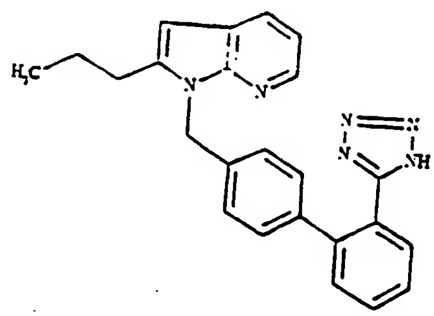
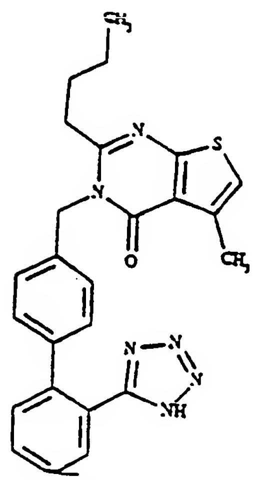
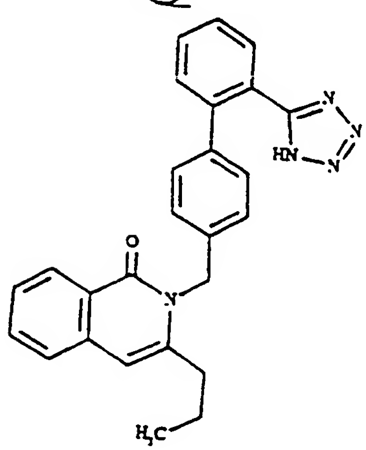
Compound #	Structure	Source
349		EP #497,516 pub. 05 Aug 92
350		EP #502,725 pub. 09 Sep 92
351		EP #502,575 pub. 09 Sep 92

TABLE II: Angiotensin II Antagonists

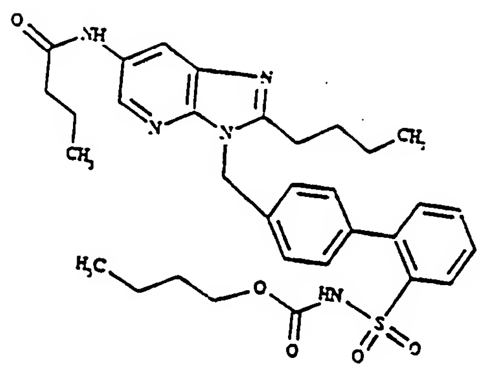
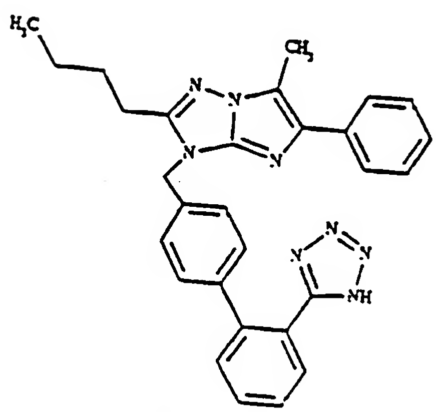
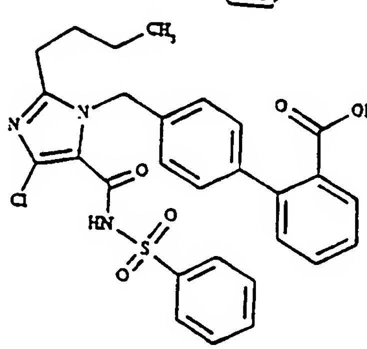
Compound #	Structure	Source
352		EP #503,838 pub. 16 Sep 92
353		EP #505,111 pub. 23 Sep 92
354		EP #505,098 pub. 23 Sep 92

TABLE II: Angiotensin II Antagonists

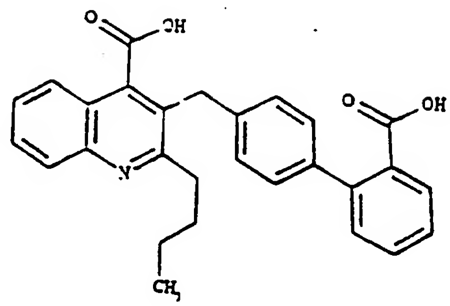
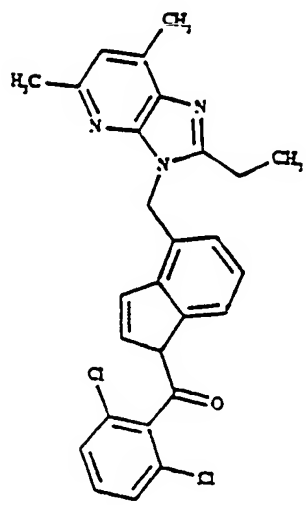
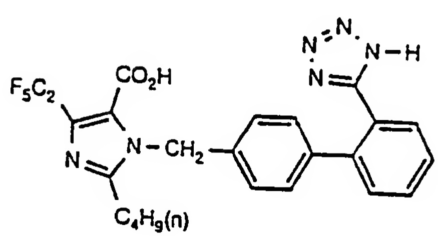
Compound #	Structure	Source
355		EP #507,594 pub. 07 Oct 92
356		EP #508,723 pub. 14 Oct 92
357		

TABLE II: Angiotensin II Antagonists

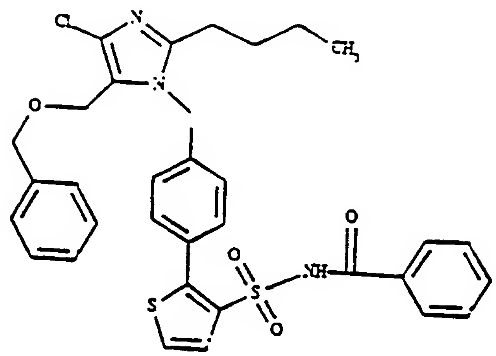
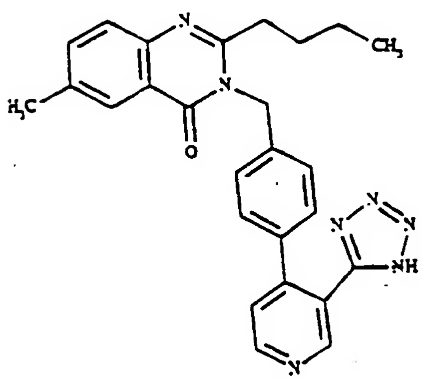
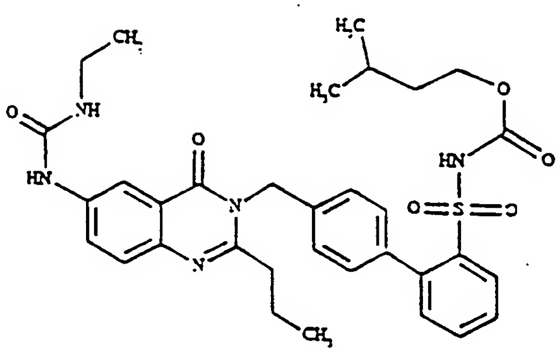
Compound #	Structure	Source
358		EP #512,675 pub. 11 Nov 92
359		EP #512,676 pub. 11 Nov 92
360		EP #512,370 pub. 11 Nov 92

TABLE II: Angiotensin II Antagonists

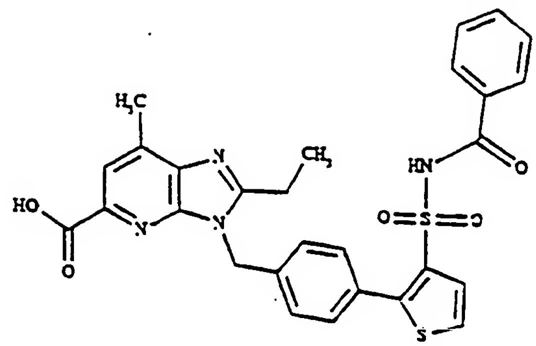
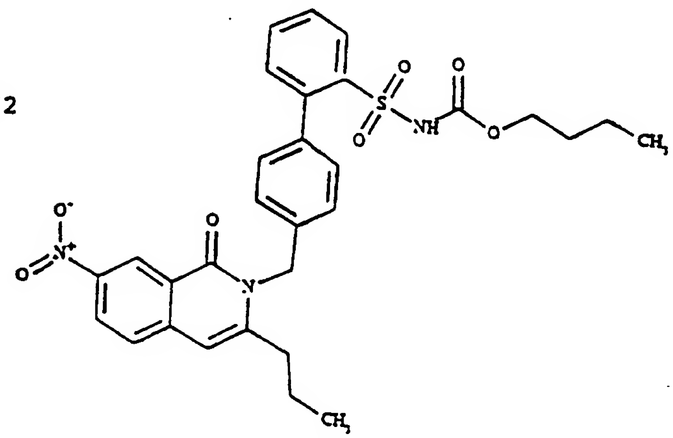
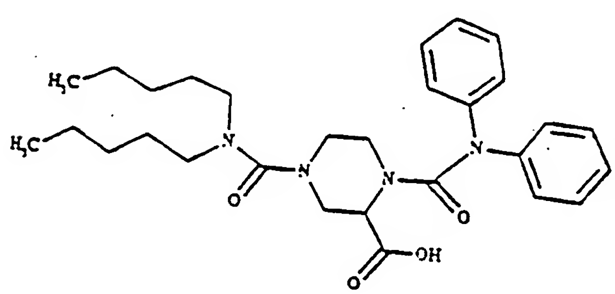
Compound #	Structure	Source
361		EP #513,979 pub. 19 Nov 92
362		WO #92/20,660 pub. 26 Nov 92
363		WO #92,20,661 pub. 26 Nov 92

TABLE II: Angiotensin II Antagonists

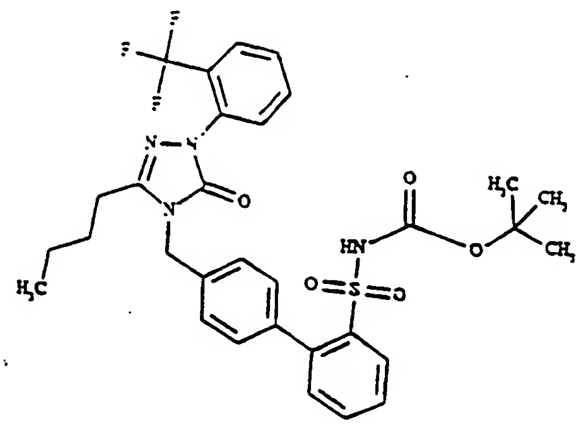
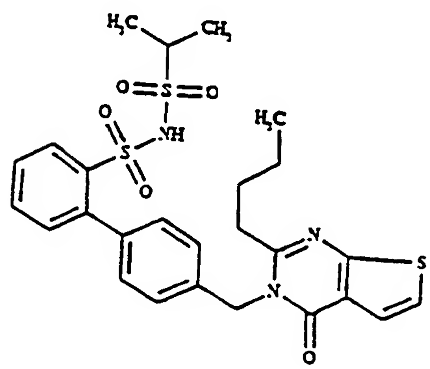
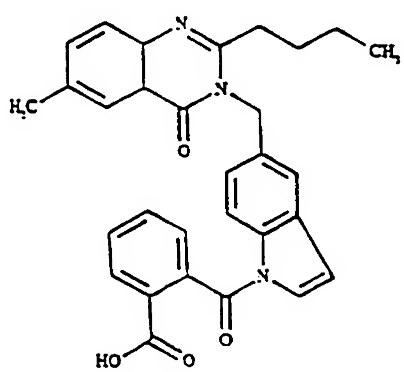
Compound #	Structure	Source
364		WO #92/20,662 pub. 26 Nov 92
365		WO #92/20,687 pub. 26 Nov 92
366		EP #517,357 pub. 09 Dec 92

TABLE II: Angiotensin II Antagonists

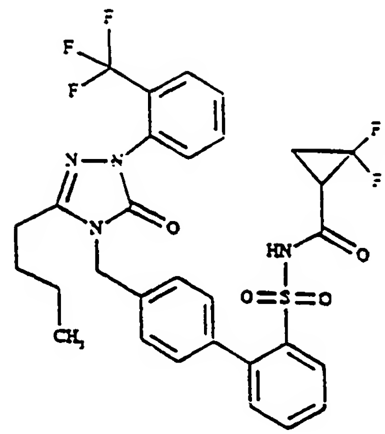
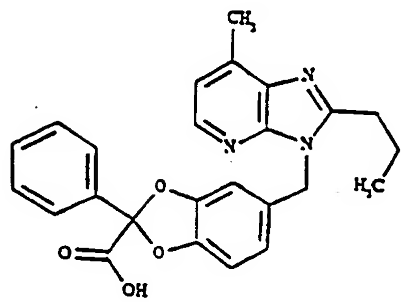
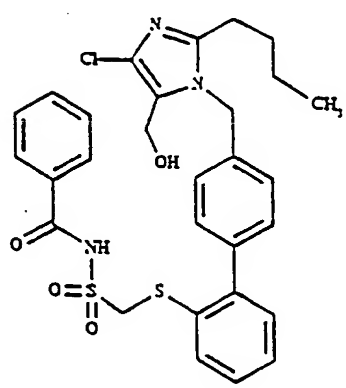
Compound #	Structure	Source
367		WO #93/01177 pub. 21 Jan 93
368		US #5,187,159 pub. 16 Feb 93
369		US #5,198,438 pub. 30 Mar 93

TABLE II: Angiotensin II Antagonists

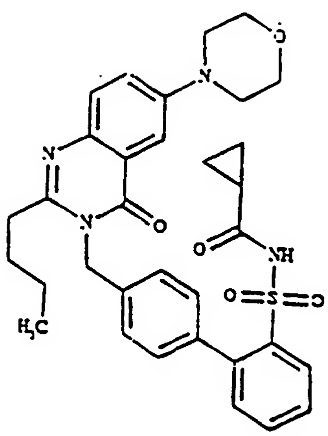
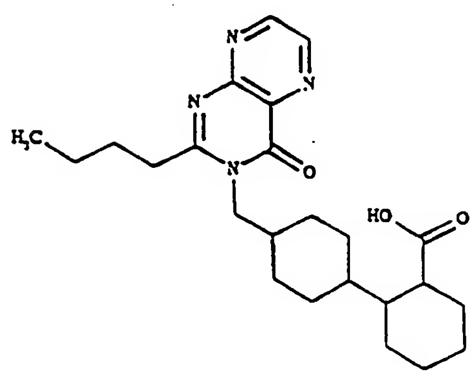
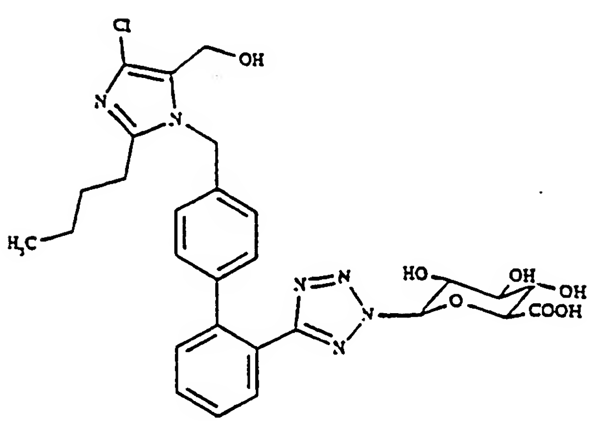
Compound #	Structure	Source
370		US #5,202,322 pub. 13 Apr 93
371		EP #537,937 pub. 21 Apr 93
372		US #5,217,882 pub. 08 Jun 93

TABLE II: Angiotensin II Antagonists

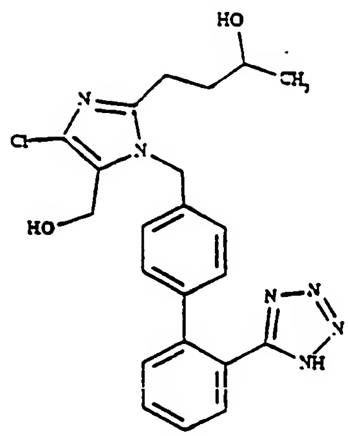
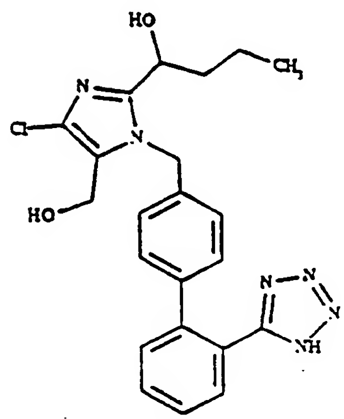
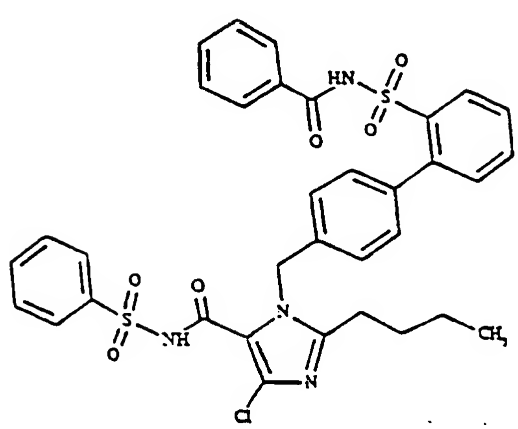
Compound #	Structure	Source
373		US #5,214,153 pub. 25 May 93
374		US #5,218,125 pub. 08 Jun 93
375		US #5,236,928 pub. 17 Aug 93

TABLE II: Angiotensin II Antagonists

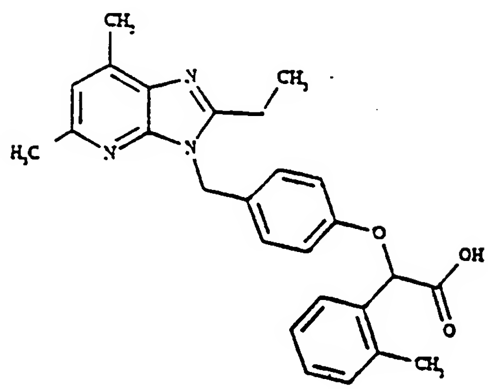
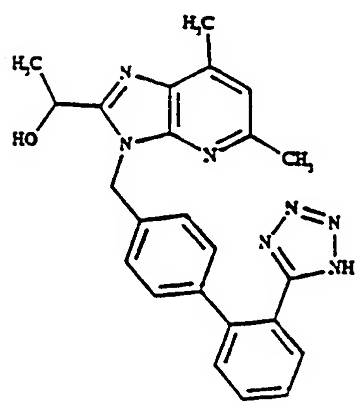
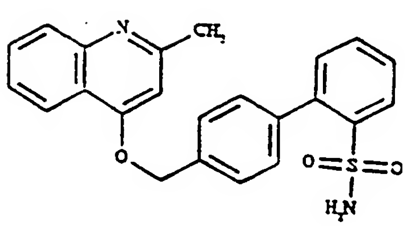
Compound #	Structure	Source
376		US #5,240,938 pub. 31 Aug 93
377		GB #2,264,709 pub. 08 Sep 93
378		GB #2,264,710 pub. 08 Sep 93

TABLE II: Angiotensin II Antagonists

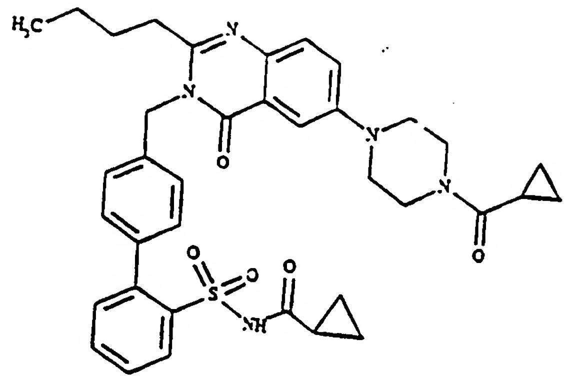
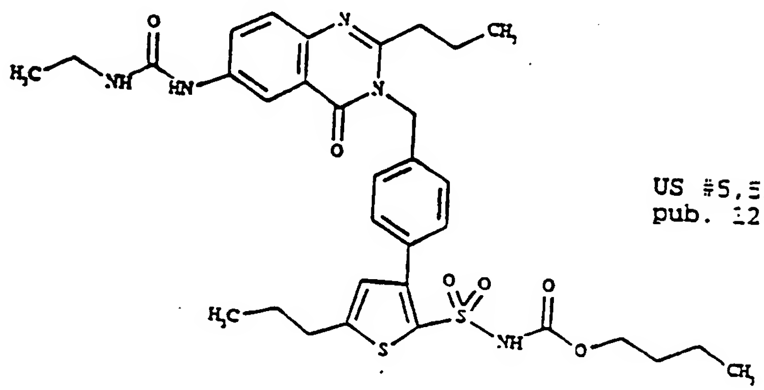
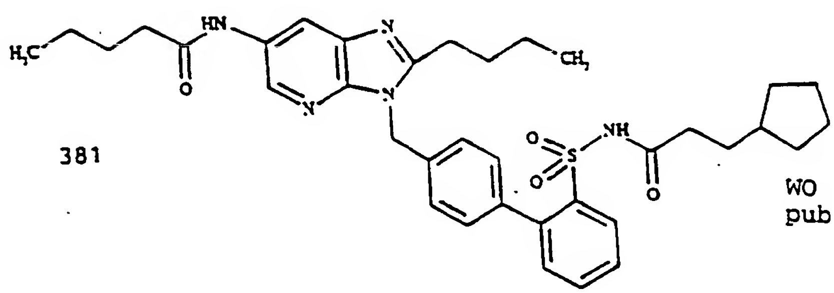
Compound #	Structure	Source
379		US #5,256,667 pub. 26 Oct 93
380		US #5,225,574 pub. 12 Oct 93
381		WO #93/23,399 pub. 25 Nov 93

TABLE II: Angiotensin II Antagonists

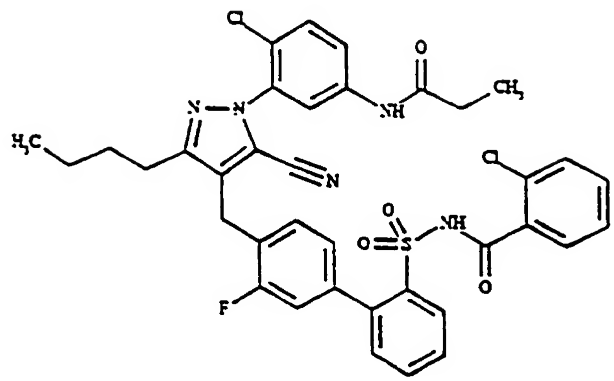
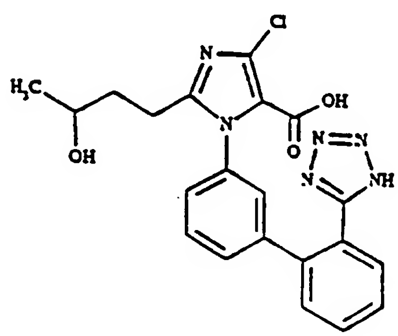
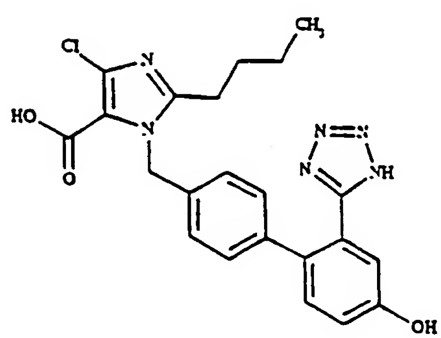
Compound #	Structure	Source
382		US #5,262,412 pub. 16 Nov 93
383		US #5,264,447 pub. 23 Nov 93
384		US #5,266,583 pub. 01 Sep 92

TABLE II: Angiotensin II Antagonists

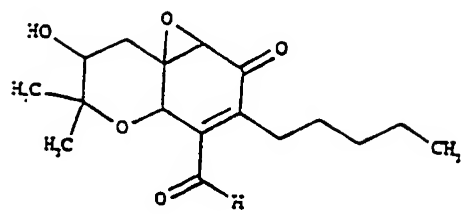
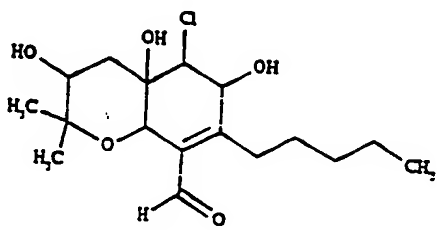
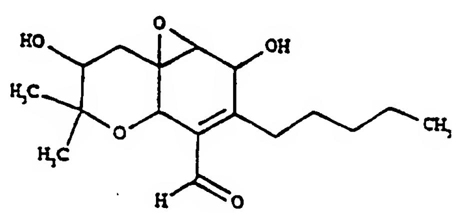
Compound #	Structure	Source
385	 	US #5,276,054 pub. 04 Jan 94
386		US #5,278,068 pub. 11 Jan 94

TABLE II: Angiotensin II Antagonists

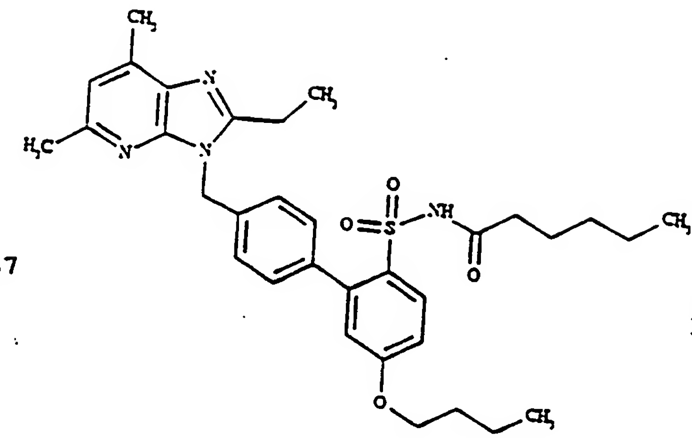
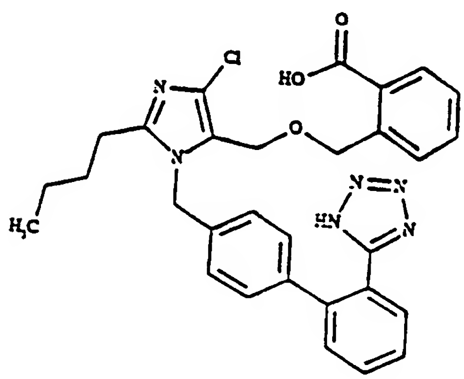
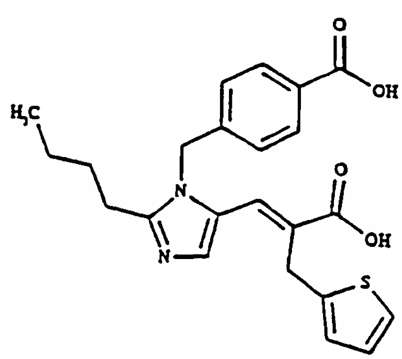
Compound #	Structure	Source
387		WO #94/02142 pub. 03 Feb 94
388		WO #94/02467 pub. 03 Feb 94
389		EP #403,159 pub. 19 Dec 90

TABLE II: Angiotensin II Antagonists

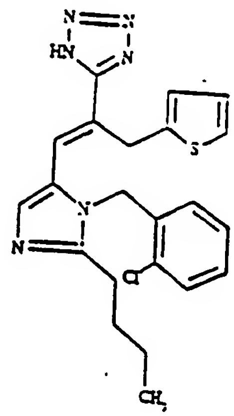
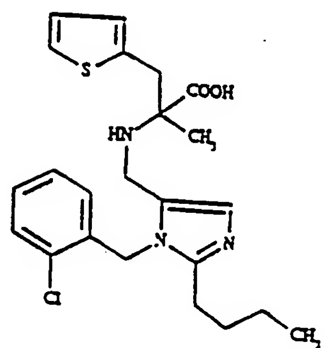
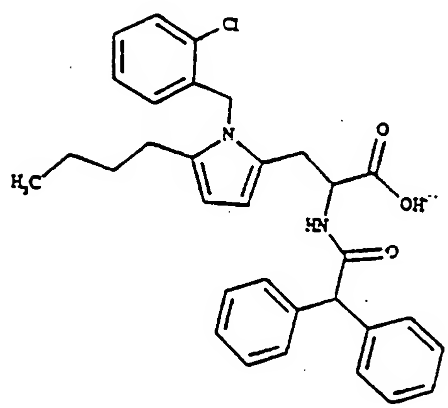
Compound #	Structure	Source
390		EP #425,211 pub. 02 May 91
391		EP #427,463 pub 15 May 91
392		WO #92/00068 pub. 09 Jan 92

TABLE II: Angiotensin II Antagonists

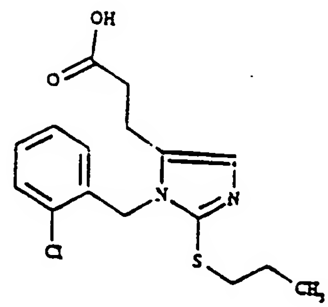
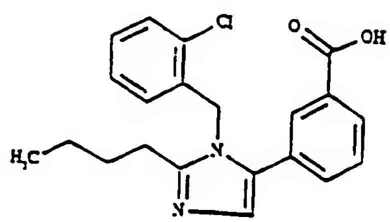
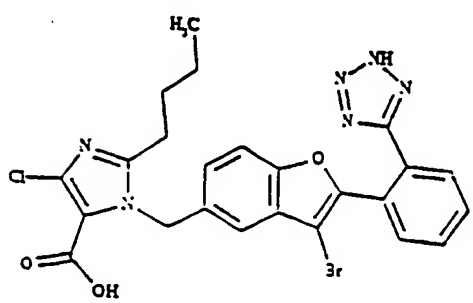
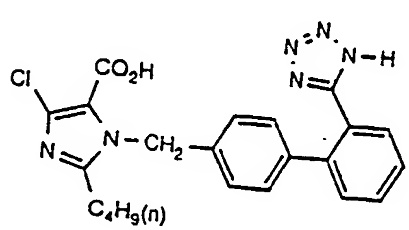
Compound #	Structure	Source
393		WO #92/02,510 pub. 20 Feb 92
394		WO #92/09278 pub. 11 Jun 92
395		WO #92/10181 pub. 25 Jun 92
396		

TABLE II: Angiotensin II Antagonists

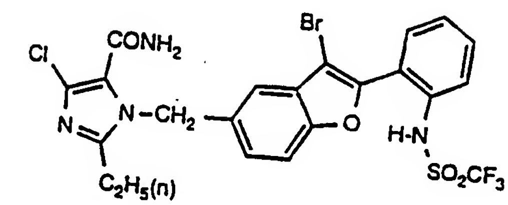
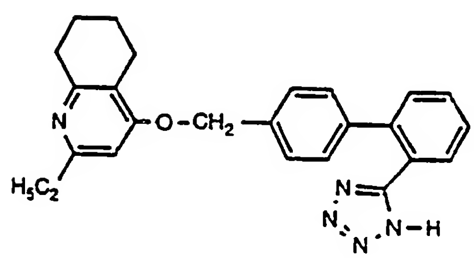
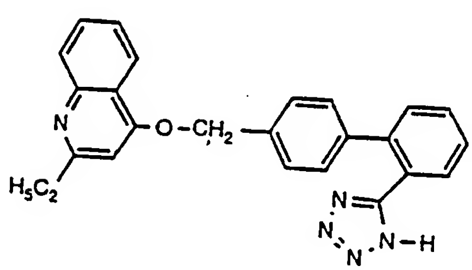
Compound #	Structure	Source
397		
398		
399		

TABLE II: Angiotensin II Antagonists

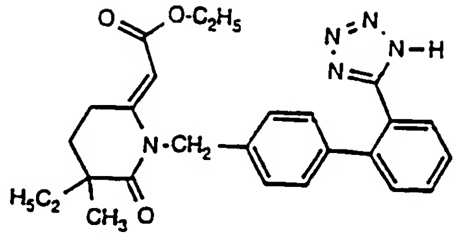
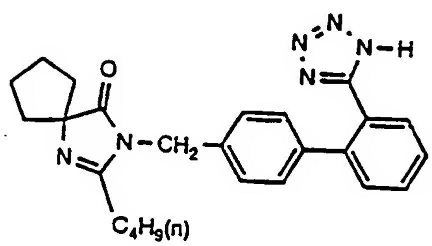
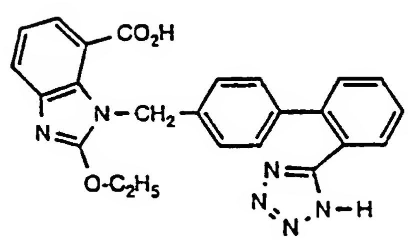
Compound #	Structure	Source
400		
401		
402		

TABLE II: Angiotensin II Antagonists

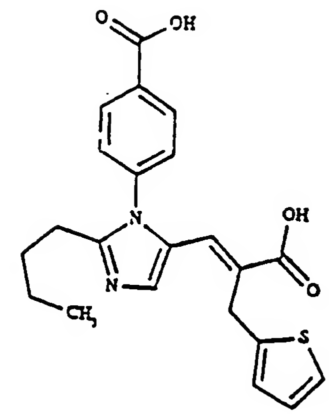
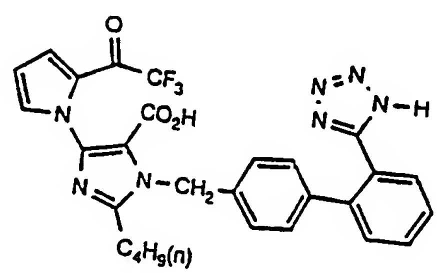
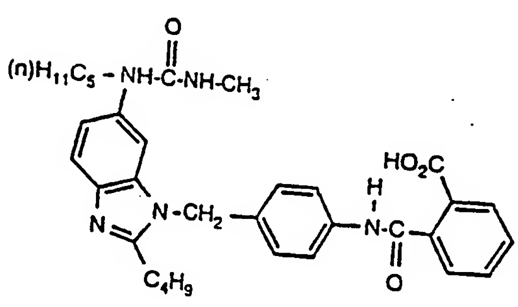
Compound #	Structure	Source
403		WO #92/10097 pub. 25 Jun 92
404		
405		

TABLE II: Angiotensin II Antagonists

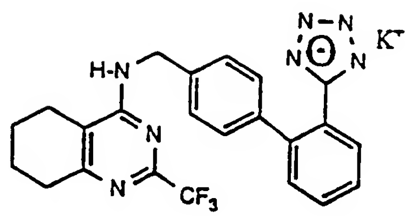
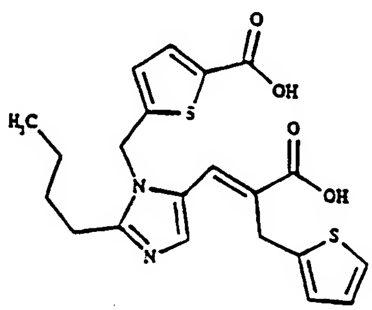
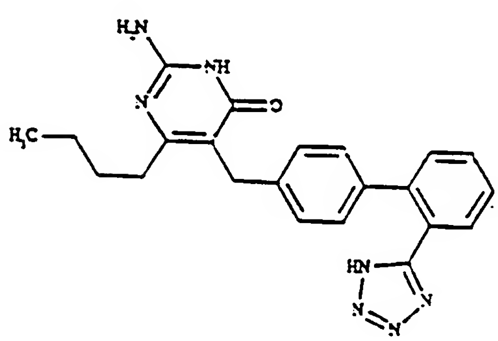
Compound #	Structure	Source
406		
407		WO #92/20651 pub. 26 Nov 92
408		WO #93/03018 pub. 18 Feb 93

TABLE II: Angiotensin II Antagonists

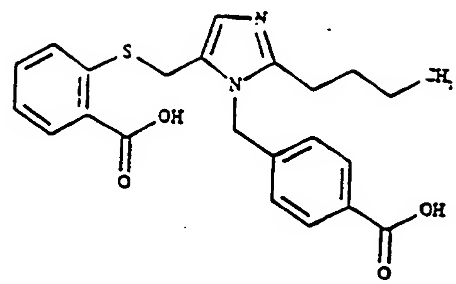
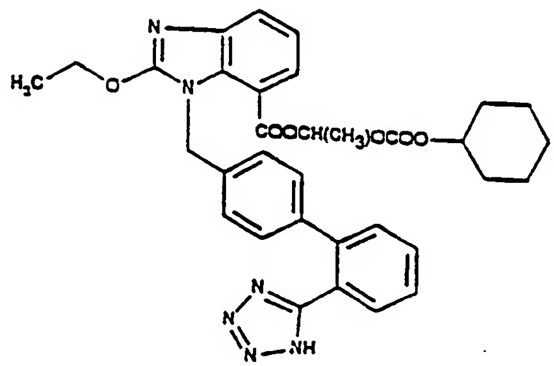
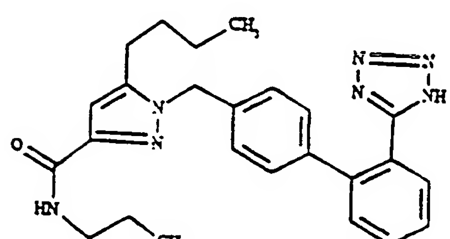
Compound #	Structure	Source
409		WO #94/00120 pub. 06 Jan 94
410		EP #459,136 pub. 04 Dec 91
411		EP #411,507 pub. 05 Feb 91

TABLE II: Angiotensin II Antagonists

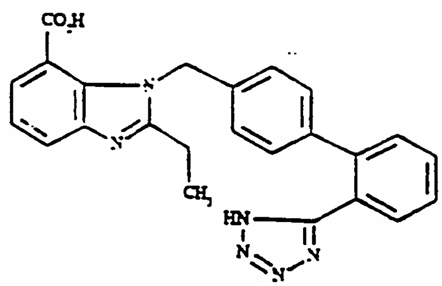
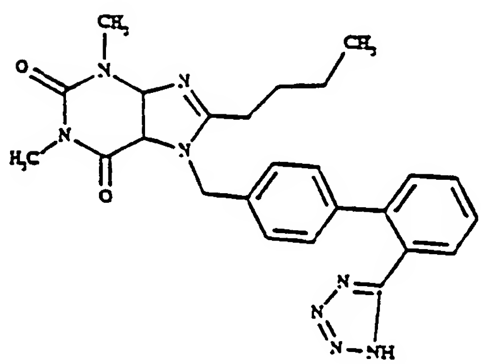
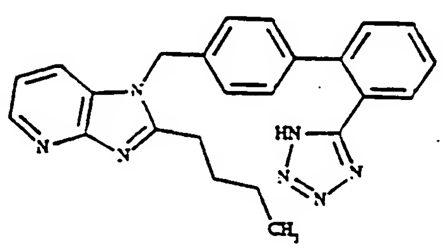
Compound #	Structure	Source
412		EP #425,921 pub. 08 May 91
413		EP #430,300 pub. 05 Jun 91
414		EP #434,038 pub. 26 Jun 91

TABLE II: Angiotensin II Antagonists

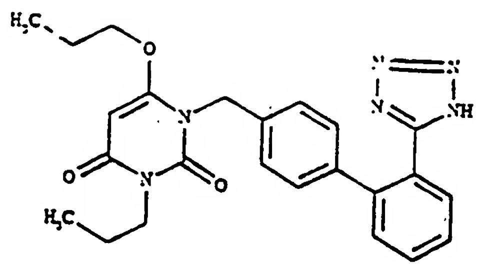
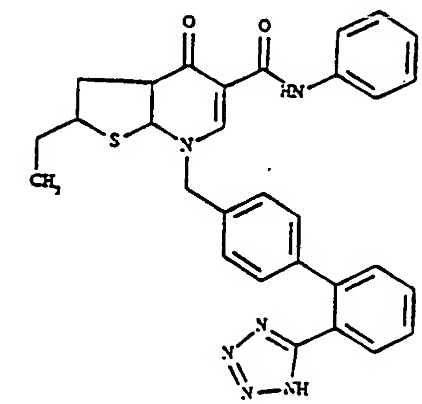
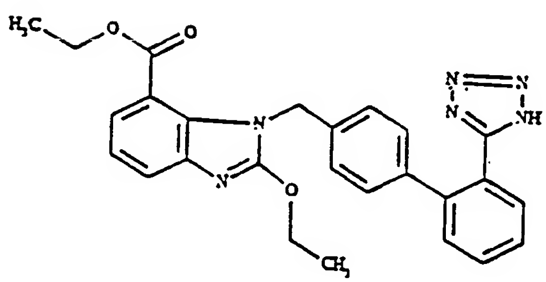
Compound #	Structure	Source
415		EP #442,473 pub. 21 Aug 91
416		EP #443,568 pub. 28 Aug 91
417		EP #459,136 pub. 04 Dec 91

TABLE II: Angiotensin II Antagonists

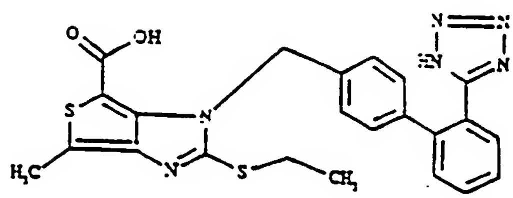
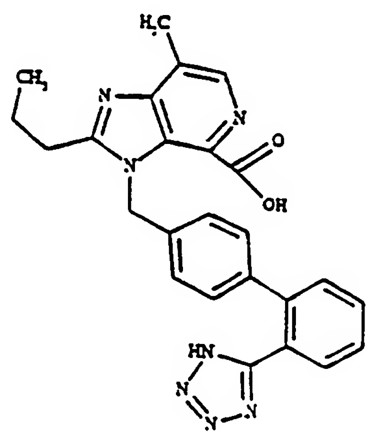
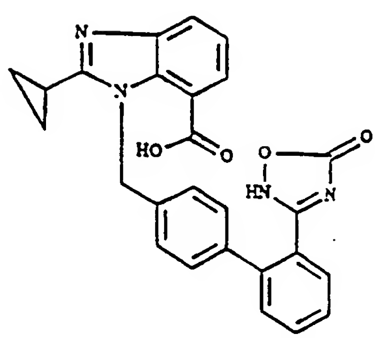
Compound #	Structure	Source
418		EP #483,683 pub. 05 May 92
419		EP #518,033 pub. 16 Dec 92
420		EP #520,423 pub. 30 Dec 92

TABLE II: Angiotensin II Antagonists

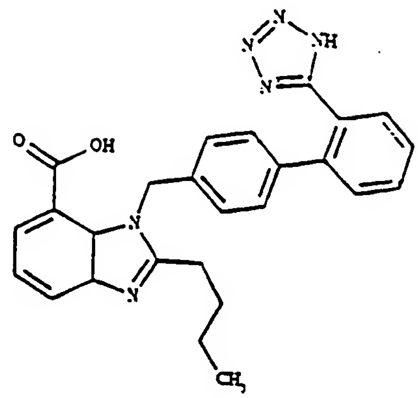
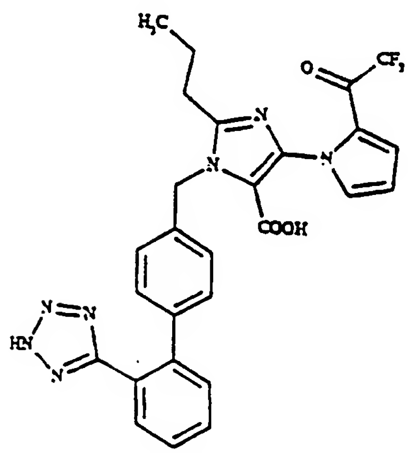
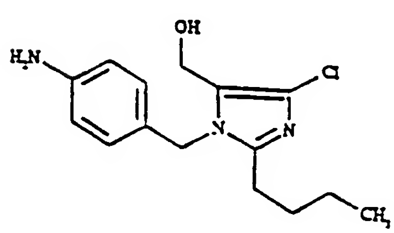
Compound #	Structure	Source
421		EP #546,358 pub. 16 Jun 93
422		WO #93/00341 pub. 07 Jan 93
423		WO #92/06081 pub. 16 Apr 92

TABLE II: Angiotensin II Antagonists

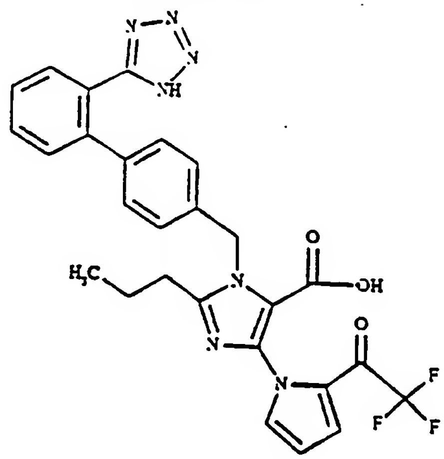
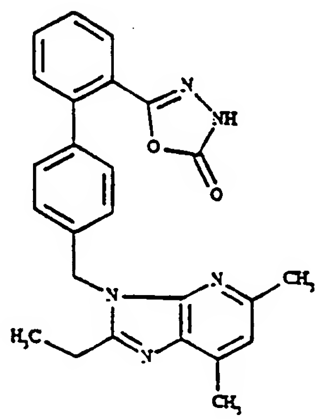
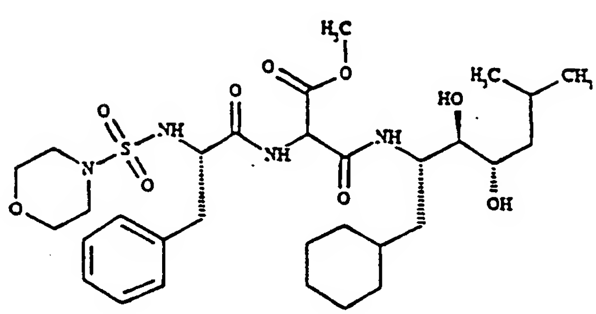
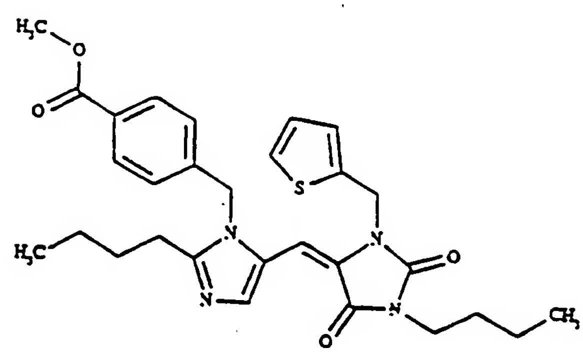
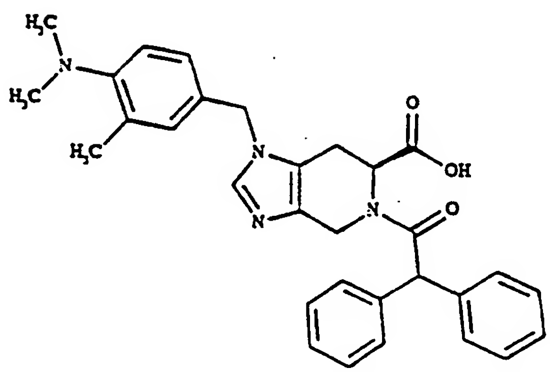
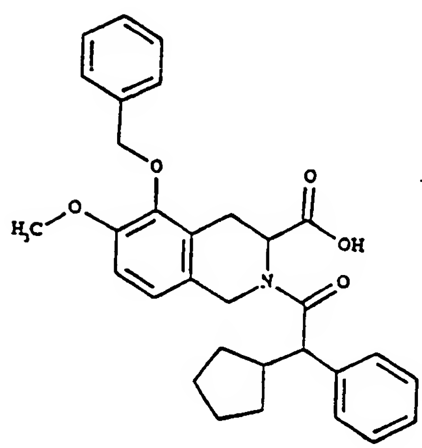
Compound #	Structure	Source
424		WO #93/00341 pub. 07 Jan 93
425		US #5,210,204 pub. 11 May 93
426		EP #343,654 pub. 29 Nov 89

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
427		WO #93/13077 pub. 08 Jul 93
428		WO #93/15734 pub. 19 Aug 93
429		US #5,246,943 pub. 21 Sep 93

The term "hydrido" denotes a single hydrogen atom (H). This hydrido group may be attached, for example, to an oxygen atom to form a hydroxyl group; or, as another example, one hydrido group may be attached to a carbon atom to form a $>CH-$ group; or, as another example, two hydrido atoms may be attached to a carbon atom to form a $-CH_2-$ group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a fluoro atom within the group. Dihaloalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two fluoro atoms, such as difluoromethyl and difluorobutyl groups, or two chloro atoms, such as a dichloromethyl group, or one fluoro atom and one chloro atom, such as a fluoro-chloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl groups. The term "difluoroalkyl" embraces alkyl groups having two fluoro atoms substituted on any one or two of the alkyl group carbon atoms. The terms "alkylol" and "hydroxyalkyl" embrace linear or branched

alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond. The term "cycloalkenyl" embraces cyclic radicals having three to about ten ring carbon atoms including one or more double bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups. The "alkoxy" or "alkoxyalkyl" radicals may be further substi-tuted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one to about ten carbon atoms attached to a divalent sulfur atom, such as a methythio group. Preferred aryl groups are those consisting of one, two, or three benzene rings. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenyl-ethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "phenalkyl" and "phenylalkyl" are interchangeable. An example of "phenalkyl" is "phenethyl" which is interchangeable with "phenylethyl". The terms "alkylaryl", "alkoxyaryl" and "haloaryl" denote, respectively, the substitution of one or more "alkyl",

"alkoxy" and "halo" groups, respectively, substituted on an "aryl" nucleus, such as a phenyl moiety. The terms "aryloxy" and "arylthio" denote radicals respectively, provided by aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes, respectively, divalent radicals SO and SO_2. The term "aralkoxy", alone or within another term, embraces an aryl group attached to an alkoxy group to form, for example, benzyloxy. The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. "Lower alkanoyl" is an example of a more prefered sub-class of acyl. The term "amido" denotes a radical consisting of nitrogen atom attached to a carbonyl group, which radical may be further substituted in the manner described herein. The term "monoalkylaminocarbonyl" is interchangeable with "N-alkylamido". The term "dialkylaminocarbonyl" is interchangeable with "N,N-dialkylamido". The term "alkenylalkyl" denotes a radical having a double-bond unsaturation site between two carbons, and which radical may consist of only two carbons or may be further substituted with alkyl groups which may optionally contain additional double-bond unsaturation. The term "heteroaryl", where not otherwised defined before, embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. Such heteroaryl may be attached as a substituent through a carbon atom of the heteroaryl ring system, or may be attached through a carbon atom of a moiety substituted on a heteroaryl ring-member carbon atom, for example, through the methylene substituent of imidazolemethyl moiety. Also, such heteroaryl may be attached through a ring nitrogen atom as long as aromaticity

of the heteroaryl moiety is preserved after attachment. For any of the foregoing defined radicals, preferred radicals are those containing from one to about ten carbon atoms.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a plurality of unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

Also included in the combination of the invention are the isomeric forms of the above-described angiotensin II receptor compounds and the epoxy-steroidal aldosterone receptor compounds, including diastereoisomers, regioisomers and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicyclic, phenylacetic, mandelic, embonic (pamoic), methansulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic,

cyclohexylaminosulfonic, stearic, algenic, β-hydroxybutyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts include metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with such compound.

BIOLOGICAL EVALUATION

In order to determine the probable effectiveness of a combination therapy for treating or preventing the progression of cardiofibrosis or cardiac hypertrophy, it is important to determine the potency of individual components of the combination therapy. Accordingly, in Assays "A" through "C", the angiotensin II receptor antagonist profiles were determined for many of the compounds described in Table II, herein. In Assay "D", there is described a method for evaluating a combination therapy of the invention, namely, an angiotensin II receptor antagonist of Table II and an epoxy-steroidal aldosterone receptor antagonist of Table I. The efficacy of each of the individual drugs, epoxymexrenone and the angiotensin II receptor blocker, and of these drugs given together at various doses, is evaluated in a rodent model. The methods and results of such assays are described below.

Assay A: Antiotensin II Binding Activity

Compounds of the invention were tested for ability to bind to the smooth muscle angiotensin II receptor using a rat uterine membrane preparation. Angiotensin II (AII) was purchased from Peninsula Labs. ^{125}I-angiotensin II (specific activity of 2200 Ci/mmol) was purchased from Du Pont-New England Nuclear. Other chemicals were obtained from Sigma Chemical Co. This assay was carried out according to the method of Douglas et al [Endocrinology, 106, 120-124 (1980)]. Rat uterine membranes were prepared from fresh tissue. All procedures were carried out at 4°C. Uteri were stripped of fat and homogenized in phosphate-buffered saline at pH 7.4 containing 5 mM EDTA. The homogenate was centrifuged at 1500 x g for 20 min., and the supernatant was recentrifuged at 100,000 x g for 60 min. The pellet was resuspended in buffer consisting of 2 mM EDTA and 50 mM

Tris-HCl (pH 7.5) to a final protein concentration of 4 mg/ml. Assay tubes were charged with 0.25 ml of a solution containing 5 mM $MgCl_2$, 2 mM EDTA, 0.5% bovine serum albumin, 50 mM Tris-HCl, pH 7.5 and ^{125}I-AII (approximately 10^5 cpm) in the absence or in the presence of unlabelled ligand. The reaction was initiated by the addition of membrane protein and the mixture was incubated at 25°C for 60 min. The incubation was terminated with ice-cold 50 mM Tris-HCl (pH 7.5) and the mixture was filtered to separate membrane-bound labelled peptide from the free ligand. The incubation tube and filter were washed with ice-cold buffer. Filters were assayed for radioactivity in a Micromedic gamma counter. Nonspecific binding was defined as binding in the presence of 10 μM of unlabelled AII. Specific binding was calculated as total binding minus nonspecific binding. The receptor binding affinity of an AII antagonist compound was indicated by the concentration (IC_{50}) of the tested AII antagonist which gives 50% displacement of the total specifically bound ^{125}I-AII from the angiotensin II AT_1 receptor. Binding data were analyzed by a nonlinear least-squares curve fitting program. Results are reported in Table III.

Assay B: In Vitro Vascular Smooth Muscle-Response for AII

The compounds of the invention were tested for antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2-2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue and then cut into 3-mm ring segments. The endothelium was removed from the rings by gently sliding a rolled-up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37°C, between moveable and fixed ends of a stainless steel wire with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled

with 20 ml of oxygenated (95% oxygen/5% carbon dioxide) Krebs solution of the following composition (mM): 130 NaCl, 15 $NaHCO_3$, 15 KCl, 1.2 NaH_2PO_4, 1.2 $MgSO_4$, 2.5 $CaCl_2$, and 11.4 glucose. The preparations were equilibrated for one hour before approximately one gram of passive tension was placed on the rings. Angiotensin II concentration-response curves were then recorded (3×10^{-10} to 1×10^{-5} M). Each concentration of AII was allowed to elicit its maximal contraction, and then AII was washed out repeatedly for 30 minutes before rechallenging with a higher concentration of AII. Aorta rings were exposed to the test antagonist at 10^{-5} M for 5 minutes before challenging with AII. Adjacent segments of the same aorta ring were used for all concentration-response curves in the presence or absence of the test antagonist. The effectiveness of the test compound was expressed in terms of pA_2 values and were calculated according to H.O. Schild [Br. J. Pharmacol. Chemother., 2, 189-206 (1947)]. The pA_2 value is the concentration of the antagonist which increases the EC_{50} value for AII by a factor of two. Each test antagonist was evaluated in aorta rings from two rabbits. Results are reported in Table III.

Assay C: In Vivo Intragastric Pressor Assay Response for AII Antagonists

Male Sprague-Dawley rats weighing 225-300 grams were anesthetized with methohexital (30 mg/kg, i.p.) and catheters were implanted into the femoral artery and vein. The catheters were tunneled subcutaneously to exit dorsally, posterior to the head and between the scapulae. The catheters were filled with heparin (1000 units/ml of saline). The rats were returned to their cage and allowed regular rat chow and water ad libitum. After full recovery from surgery (3-4 days), rats were placed in Lucite holders and the arterial line was connected to a pressure transducer. Arterial pressure was recorded on a Gould polygraph (mmHg). Angiotensin II was administered as a 30

ng/kg bolus via the venous catheter delivered in a 50 µl volume with a 0.2 ml saline flush. The pressor response in mm Hg was measured by the difference from pre-injection arterial pressure to the maximum pressure achieved. The AII injection was repeated every 10 minutes until three consecutive injections yielded responses within 4 mmHg of each other. These three responses were then averaged and represented the control response to AII. The test compound was suspended in 0.5% methylcellulose in water and was administered by gavage. The volume administered was 2 ml/kg body weight. The standard dose was 3 mg/kg. Angiotensin II bolus injections were given at 30, 45, 60, 75, 120, 150, and 180 minutes after gavage. The pressor response to AII was measured at each time point. The rats were then returned to their cage for future testing. A minimum of 3 days was allowed between tests. Percent inhibition was calculated for each time point following gavage by the following formula: [(Control Response - Response at time point)/Control Response] X 100. Results are shown in Table III.

Assay "D": Renal Hypertensive Rat Model

A combination therapy of an angiotensin II receptor antagonist and an epoxy-steroidal aldosterone receptor antagonist may be evaluated for blood pressure lowering activity in the renal-artery ligated hypertensive rat, a model of high renin hypertension. In this model, six days after ligation of the left renal artery, both plasma renin activity and blood pressure are elevated significantly [J.L. Cangiano et al, J. Pharmacol. Exp. Ther., 206, 310-313 (1979)]. Male Sprague-Dawley rats are instrumented with a radiotelemetry blood pressure transmitter for continuous monitoring of blood pressure. The rats are anesthetized with a mixture of ketamine-HCl (100 mg/kg) and acepromazine maleate (2.2 mg/kg). The abdominal aorta is exposed via a midline incision. Microvascular clamps are placed on the

aorta distal to the renal arteries and at the iliac bifurcation. The aorta is punctured with a 22-guage needle and the tip of a catheter is introduced. The catheter, which is held in place by a ligature in the psoas muscle, is connected to a radiotelemetry blood pressure transmitter (Mini-Mitter Co., Inc., Sunriver, OR). The transmitter is placed in the peritoneal cavity and sutured to abdominal muscle upon closing of the incision. Rats are housed singly above a radiotelemetry receiver and are allowed standard rat chow and water *ad libitum*. At least 5 days are allowed for recovery from surgery. Mean arterial pressure and heart rate are measured on a Compaq DeskPro 286 AT computer. Data are sampled for 10 seconds at 200-500 hz at 2.5 to 10 min intervals 24 hours per day. After collecting control data for 24 hours, the rats are anesthetized with methohexital (30 mg/kg, i.p.) and supplemented as needed. A midline abdominal incision is made, approximately 2cm in length to expose the left kidney. The renal artery is separated from the vein near the aorta, with care taken not to traumatize the vein. The artery is completely ligated with sterile 4-O silk. The incision is closed by careful suturing of the muscle layer and skin. Six days later, when MAP is typically elevated by 50-70 mmHg, an AII receptor antagonist, or an aldosterone receptor antagonist, or a combination of the two compounds are administered by gavage each day for about 8 weeks. Single drug dosing is carried out using 20 and 200 mg/kg/day of epoxymexrenone and 1,3,10,30 and 100 mg/kg/day of an AII receptor antagonist. Drug mixtures are obtained by administering a combination of a dose of 1,3,10,30 or 100 mg/kg/day of the AII receptor antagonist with a dose of either 20 or 200 mg/kg/day of the aldosterone antagonist. Blood pressure lowering is monitored by the radiotelemetry system and responses with the compounds are compared to responses obtained in vehicle-treated animals. Plasma and urinary sodium and potassium levels are monitored as a measure of the effectiveness of the aldosterone blockade. Urine samples are collected

overnight using metabolic cages to isolate the samples. Plasma samples are obtained by venous catheterization. Sodium and potassium are measured by flame photometry. Cardiac fibrosis is determined by histological and chemical measurements of the excised hearts following perfusion fixation. Left and right ventricles are weighed, embedded and sectioned. Subsequently, sections are stained with picrosirius red and the red staining collagen areas are quantitated by computerized image analysis. The apex of the heart is acid digested and the free hydroxyproline measured colorimetrically. It is expected that MAP will be significantly lowered toward normal pressures in the test animals, treated with the combination therapy and that the condition of myocardial fibrosis will be arrested or avoided.

TABLE III

In Vivo and In Vitro Angiotensin II Activity of Compounds of the Invention

Test Compound Example #	[1]Assay A IC_{50} (nM)	[2]Assay B pA_2	[3]Assay C Dose (mg/kg)	Inhibition (%)	Duration (min.)
1	NT	NT	NT	NT	NT
2	95	7.37/7.59	10	95	60
			30	98	90-120
3	5.4	8.70 ± 0.2	10	50	>180
			30	100	200^{+}
4	NT	NT	NT	NT	NT
5	200	7.48/6.91	30	38	20-30
6	1300	6.55/6.82	100	90	120
7	84	8.01/8.05	30	90	130
8	17,000	NT	NT	NT	NT
9	700	6.67/6.12	30	80	75
			100	100	130
10	4.9	8.19/7.59	3	86	100
			30	100	240
11	160	6.45/6.77	NT	NT	NT
12	6.0	8.66/8.59	NT	NT	NT
13	17	8.70/8.85	NT	NT	NT
14	7.2	8.84/8.71	NT	NT	NT
15	16	8.31/8.30	NT	NT	NT
16	6.4	8.95/9.24	NT	NT	NT
17	4.0	8.64/8.40	NT	NT	NT
18	970	6.14/6.09	NT	NT	NT
19	12,000	5.18/5.35	NT	NT	NT

Test Compound Example #	[1]Assay A IC_{50} (nM)	[2]Assay B pA_2	Dose (mg/kg)	[3]Assay C Inhibition (%)	Duration (min.)
20	78,000	5.89/5.99	100	10	45
21	87	7.71.7.21	NT	NT	NT
22	460	6.60/6.46	NT	NT	NT
23	430	6.48/7.15	NT	NT	NT
24	10	7.56/7.73	NT	NT	NT
25	480	6.80/6.73	NT	NT	NT
26	3.2	9.83/9.66	10	50	>180
27	180	NT	NT	NT	NT
28	570	5.57/6.00	NT	NT	NT
29	160	NT	NT	NT	NT
30	22	7.73/7.88	30	50	>180
31	14	NT	NT	NT	NT
32	16	7.68/7.29	NT	NT	NT
33	630	6.73/6.36	NT	NT	NT
34	640	5.34/5.69	NT	NT	NT
35	41	7.25/7.47	NT	NT	NT
36	1400	5.92/5.68	NT	NT	NT
37	340	6.90/6.85	NT	NT	NT
38	10	7.82/8.36	NT	NT	NT
39	10	7.88/7.84	NT	NT	NT
40	83	7.94/7.61	NT	NT	NT
41	3700	5.68/5.96	NT	NT	NT
42	370	6.56/6.26	NT	NT	NT
43	19	8.97/8.61	NT	NT	NT
44	16	8.23/7.70	NT	NT	NT
45	4.4	8.41/8.24	NT	NT	NT
46	110	6.80/6.64	NT	NT	NT

Test Compound Example #	[1]Assay A IC$_{50}$ (nM)	[2]Assay B pA$_2$	[3]Assay C Dose (mg/kg)	Inhibition (%)	Duration (min.)
47	21	7.85/7.58	NT	NT	NT
48	680	6.27/6.75	NT	NT	NT
49	120	7.06/7.07	NT	NT	NT
50	54	7.71/7.89	NT	NT	NT
51	8.7	8.39/8.51	NT	NT	NT
52	100	8.14/8.12	NT	NT	NT
53	65	7.56/7.83	NT	NT	NT
54	3100	6.02	NT	NT	NT
55	80	6.56/7.13	NT	NT	NT
56	5.0	9.04/8.35	NT	NT	NT
57	2300	6.00	NT	NT	NT
58	140	6.45/6.57	NT	NT	NT
59	120	7.23/7.59	NT	NT	NT
60	2200	6.40/6.03	NT	NT	NT
61	110	7.29/7.70	NT	NT	NT
62	26	8.69/8.61	NT	NT	NT
63	61	7.77/7.67	NT	NT	NT
64	54	7.00/6.77	NT	NT	NT
65	23	7.85/7.75	NT	NT	NT
66	12	9.34/8.58	NT	NT	NT
67	3100	5.88/5.78	NT	NT	NT
68	8.6	8.19/8.65	NT	NT	NT
69	15	7.80/8.28	NT	NT	NT
70	44	7.71/8.05	NT	NT	NT
71	12,000	*	NT	NT	NT
72	83	6.11/6.10	NT	NT	NT
73	790	7.65/7.46	NT	NT	NT

Test Compound Example #	[1]Assay A IC_{50} (nM)	[2]Assay B pA_2	[3]Assay C Dose (mg/kg)	Inhibition (%)	Duration (min.)
74	6.5	8.56/8.39	NT	NT	NT
75	570	6.00/5.45	NT	NT	NT
76	5400	5.52/5.78	NT	NT	NT
77	15,000	5.77	NT	NT	NT
78	101	7.0		93	60-100
79	4.9	9.2		100	>200
				50	>180
80	25	8.1		NT	NT
81	18	8.0		40	180
82	7.9	8.5		20	180
83	3.6	8.3		15	>180
84	16	7.1		20	30
85	8.7	8.9		NT	NT
86	9	7.8		NT	NT
87	91	7.8		NT	NT
88	50	7.7		NT	NT
89	18	7.9		NT	NT
90	5.6	9.0		NT	NT
91	30	8.6		40	>180
92	35	7.9		NT	NT
93	480	NT		NT	NT
94	5,800	NT		NT	NT
95	66	8.2		NT	NT
96	21	8.0		NT	NT
97	280	7.7		NT	NT
98	22	8.1		NT	NT
99	280	6.5		NT	NT
100	4.4	9.4		NT	NT
101	36	7.8		NT	NT

Test Compound Example #	[1]Assay A IC$_{50}$ (nM)	[2]Assay B pA$_2$	[3]Assay C Dose (mg/kg)	Inhibition (%)	Duration (min.)
102	43	7.7		NT	NT
103	12	8.0		NT	NT
104	15	8.0		NT	NT
105	290	6.6		NT	NT
106	48	7.7		NT	NT
107	180	8.3		NT	NT
108	720	5.3	100	45	90
109	250	7.3	30	50	30
110	590	6.4		NT	NT
111	45	9.0	30	87	160
112	2000	5.2		NT	NT
113	12	8.4	10	60	180
114	400	6.4		NT	
115	11	8.2	3	40	>240
116	230	6.5		NT	
117	170	6.5		NT	
118	37	9.21/9.17	10	70	120
119	16	9.21/9.00	3	20	60
120	25	9.05/8.77	10	80	240
121	46	NT		NT	
122	46	NT		NT	
123	50	NT		NT	
124	40	9.42/9.12	3	45	>180
125	40	9.25/8.80	3	35	>240

Test	[1]Assay A	[2]Assay B		[3]Assay C	
Compound	IC_{50}	pA_2	Dose	Inhibition	Duration
Example #	(nM)		(mg/kg)	(%)	(min.)
126	240	7.20/7.05		NT	
127	12,000	4.96		NT	
128	16	8.63/8.40		NT	
129	6,700	5.30		NT	
130	40	8.10/7.94		NT	
131	9.5	7.53/8.25			
132	12	8.6		NT	
133	10	8.7	3	20	180
					90-120
134	22	9.3	3	35	180
135	16	8.5	3	35	>180
136	NT	NT		NT	
137	220	8.3		NT	
138	130	8.2		NT	
139	0.270	6.3		NT	
140	0.031	8.1		100	160
141	0.110	8.02		NT	NT
142	2.000	NA		NT	NT
143	0.052	7.7		85	75
144	0.088	7.7		50	125
145	0.480	6.7		NT	NT
146	0.072	6.4		NT	NT

Test Compound Example #	[1]Assay A IC_{50} (nM)	[2]Assay B pA_2	[3]Assay C Dose (mg/kg)	Inhibition (%)	Duration (min.)
147	5.8	5.6	3	74	5-10
148	0.87	5.8	3	92	20-30
149	1.1	6.1	3	NT	NT
150	14	8.03/7.80	3	25	>180
151	17	7.76/7.97	3	15	180
152	150	7.46/7.23	3	10	140
153	13	8.30/7.69	3	25	>180
154	97	8.19/8.38		NA	
155	86	7.60/7.14		NA	
156	78	8.03/7.66		NA	
157	530	- /6.22		NA	
158	54	8.23/8.14	3	30	>180
159	21	7.92/7.56	3	10	150
160	64	7.87/7.71			
161	28			NA	
162	380	6.21/6.55		NA	
163	420	7.42/6.75		NA	
164	1700			NA	
165	410	6.90/7.18		NA	

Test Compound Example #	[1]Assay A IC$_{50}$ (nM)	[2]Assay B pA$_2$	[3]Assay C Dose (mg/kg)	Inhibition (%)	Duration (min.)
166	160	7.57/7.74		NA	
167	370	7.08/7.11		NA	
168	420	7.69/7.58		NA	
169	150	7.78/7.58	3	15	180
170	26	7.08/7.77	3	40	>180
171	28	7.52/7.11	3	0	0
172	70	7.15/7.04		NA	
173	90	7.49/6.92		NA	
174	180	7.29/7.02		NA	
175	27	NA	3	0	0
176	9.8	7.69/7.55	3	10	150
177	26	7.41/7.85	3	15	180
178	88	7.54/7.47		NA	
179	310	6.67/ -		NA	
180	20	7.56/7.15	3	25	180
181	21	7.70/7.12	3	20	180
182	59	NA		NA	
183	390	NA		NA	
184	1100	6.78/ -		NA	

Test Compound Example #	[1]Assay A IC$_{50}$ (nM)	[2]Assay B pA$_2$	Dose (mg/kg)	[3]Assay C Inhibition (%)	Duration (min.)
185	6.5	8.82/8.53	3	50	> 180
186	38	8.13/7.40	3	25	180
187	770	7.46/6.95		NA	
188	140	7.72/7.09		NA	
189	29	8.64/8.23		NA	
190	10	7.87/7.89	3	10	180
191	81	7.75/7.76	3	10	180
192	140			NA	
193	11	9.27/8.87	3	10	180
194	47	7.64/7.35		NA	
195	34	8.44/8.03		NA	
196	31	7.68/8.26		NA	
197	14	8.03/8.60		NA	
198	7.6	8.76/8.64	3	35	> 180
199	10	8.79/8.85	3	60	> 180
200	20	8.42/8.77	3	45	> 180
201	17	8.78/8.63	3	10	180
202	12	8.79/8.64	3	65	> 180
203	9.2	8.43/8.36	3	50	> 180
204	16	9.17/8.86	3	75	> 180
205	20	9.14/9.15	3	40	> 180
206	5.4	8.75/8.89	3	30	> 180
207	99	9.04/8.60		NA	
208	22	9.19/8.69	3	50	> 180
209	5.0	9.41/9.16	3	25	> 180
210	3.6	8.36/8.44	3	15	180
211	18	8.74/8.67	3	35	> 180
212	23	8.85/8.25	3	15	180
213	51	NA		NA	
214	65	NA		NA	
215	45	NA		NA	
216	5.4	8.80/9.04	3	50	> 180

Test Compound Example #	[1]Assay A IC_{50} (nM)	[2]Assay B pA_2	[3]Assay C Dose (mg/kg)	Inhibition (%)	Duration (min.)
217	9.4	NA	3	65	> 180
218	9.0	NA		NA	
219	14	NA		NA	
220	7.0	NA	3	75	120
221	4.8	NA	3	25	> 180
222	5.0	NA		NA	
223	14	7.45/7.87	3	20	> 180
224	91	NA		NA	
225	160	NA		NA	
226	93	NA		NA	
227	89	7.55/7.67		NA	
228	4.5	9.17/8.25	3	80	>180
229	19	NT	3	40	>180
230	2.6	8.23/8.69	3	25	>180
231	3.6	NT	3	75	>180
232	4.4	8.59/8.89	3	70	>180
233	84	8.51/8.78		NT	
234	5.0	8.49/9.00	3	20	-
235	34	7.14/7.07		NT	
236	4.9	NC	3	70	>180
237	3.6	NT		NT	
238	1.7	NT	3	15	>180
239	6.8	7.88/8.01	3	20	>180
240	120	NA		NA	
241	6.9	8.57/8.24	3	40	>180
242	110	7.11/6.60		NA	
243	250	NA		NA	
244	150	7.17/7.17		NA	
245	98	6.64/7.04		NA	
246	72	7.46/7.59		NA	
247	9.4	8.26/8.41	3	20	180

Test Compound Example #	[1]Assay A IC$_{50}$ (nM)	[2]Assay B pA$_2$	Dose (mg/kg)	[3]Assay C Inhibition (%)	Duration (min.)
248	20	7.68/7.50	3	10	--
249	4.4	NA	3	20	>180
250	43	NA	3	0	--
251	25	NA		NA	
252	13	NA		NA	
253	2.6	NA		NA	
254	72	NA		NA	
255	12	7.61/7.46	3	20	>180
256	4.1	8.43/7.78	3	30	>180
257	160	6.63/6.68		NA	
258	350	6.84/6.84		NA	
259	54	NA		NA	
260	220	NA		NA	
261	18	NA		NA	
262	530	-/6.22		NA	
263	57	NA		NA	
264	11	NA		NA	
265	110	NA		NA	
266	290	NA		NA	
267	25	NA	3	25	>180
268	520	NA	3	0	--
269	9.7	NA		NA	
270	21	NA		NA	
271	14	NC	3	20%	--
272	97	NC	3	70%	>180 min.
273	9.8	8.53/8.61	3	25%	>180 min.
274	13	9.06/8.85	3	35%	>180 min.
275	6.3	9.07/ --	3	40%	>180 min.
276	33	8.71/8.64	3	<20%	
277	190	-- /6.54		NT	
278	30	8.49/8.51	3	50%	>180 min.
279	270	8.06/8.25		NT	
280	480	6.41/6.35	NT	NT	NT

NT = NOT TESTED

NC = Non-Competitive antagonist

*Antagonist Activity not observed up to 10 µM of test compound.

1Assay A: Angiotensin II Binding Activity

2Assay B: In Vitro Vascular Smooth Muscle Response

3Assay C: In Vivo Pressor Response

Test Compounds administered intragastrically, except for compounds of examples #1-#2, #4-#25, #27-#29, #30-#79, #108-#109, #111, #118 and #139-#149 which were given intraduodenally.

Administration of the angiotensin II receptor antagonist and the aldosterone receptor antagonist may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or separate formulations. Administration may be accomplished by oral route, or by intravenous, intramuscular or subcutaneous injections. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropyl-methyl cellulose, together with one or more of a lubricant, preservative, surface-active or dispersing agent.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of each active ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.01 to 30 mg/kg body weight, particularly from about 1 to 15 mg/kg body weight, may be appropriate.

The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose of each active component is from about 0.01 to 15 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred

daily dose would be from about 1 to 10 mg/kg body weight. Compounds indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 15 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 15 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 10 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

In combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 5 mg to about 400 mg, and the AII antagonist may be present in an amount in a range from about 1 mg to about 800 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 400:1 to about 1:160.

In a preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 10 mg to about 200 mg, and the AII antagonist may be present in an amount in a range from about 5 mg to about 600 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 40:1 to about 1:60.

In a more preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 20 mg to about 100 mg, and the AII antagonist may be present in an amount in a range from about 10 mg to about 400 mg, which represents aldosterone

antagonist-to-AII antagonist ratios ranging from about 10:1 to about 1:20.

The dosage regimen for treating a disease condition with the combination therapy of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

For therapeutic purposes, the active components of this combination therapy invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the components may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The components may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What Is Claimed Is:

1. A method to treat a subject susceptible to or afflicted with cardiofibrosis or cardiac hypertrophy, which method comprises administering a combination of drug agents comprising a therapeutically-effective amount of an angiotensin II receptor antagonist and a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist.

2. The method of Claim 1 wherein said epoxy-steroidal aldosterone receptor antagonist is selected from epoxy-containing compounds.

3. The method of Claim 2 wherein said epoxy-containing compound has an epoxy moiety fused to the "C" ring of the steroidal nucleus of a 20-spiroxane compound.

4. The method of Claim 3 wherein said 20-spiroxane compound is characterized by the presence of a 9α-,11α-substituted epoxy moiety.

5. The method of Claim 2 wherein said epoxy-containing compound is selected from the group consisting of

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo,γ-lactone, methyl ester, (7α,11α,17α)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester,(7α,11α,17α)-;

3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,γ-lactone,(6β,7β,11β,17β)-;

pregn-4-ene-7,21-dicarboxylic acid,9,11-

epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester, monopotassium salt,(7α,11α,17α)-;

pregn-4-ene-7,21-dicarboxylic acid,9,11,-epoxy-17-hydroxy-3-oxo-,7-methyl ester, monopotassium salt, (7α,11α,17α)-;

3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,γ-lactone(6α,7α,11.α)-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6α,7α,11α,17α)-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6α,7α,11α,17α)-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,γ-lactone, (6α,7α,11α.,17α)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,γ-lactone, ethyl ester, (7α,11α,17α)-; and

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,γ-lactone, 1-methylethyl ester,(7α,11α,17α)-.

6. The method of Claim 1 wherein said angiotensin II receptor antagonist is selected from compounds consisting of a first portion and a second portion, wherein said first portion is selected from a fragment of Formula I:

Ar-Alk-L
Ar-L-Ar-Alk-L
Het-L-Ar-Alk-L
Het-L-Het-Alk-L (I)
Ar-L-Het-Alk-L
Het-L-Alk-L

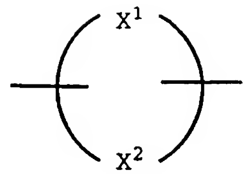
wherein Ar is a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being fully unsaturated or partially or fully saturated;

wherein Het is a monocyclic or bicyclic fused ring system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from one or more hetero atoms selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as ring members;

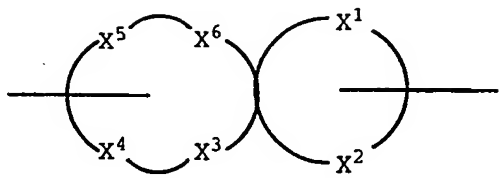
wherein Alk is an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms;

wherein L is a straight bond or a bivalent linker moiety selected from carbon, oxygen and sulfur;

and wherein said second portion is a monocyclic heterocyclic moiety selected from moieties of Formula IIa or is a bicyclic heterocyclic moiety selected from moieties of Formula IIb:



(IIa)



(IIb)

wherein each of X^1 through X^6 is selected from -CH=, $-CH_2-$, -N=, -NH-, O, and S, with the proviso that at least one of X^1 through X^6 in each of Formula IIa and Formula IIb must be a hetero atom, and wherein said heterocyclic moiety of Formula IIa or IIb may be attached through a bond from any ring member of the Formula IIa or IIb heterocyclic moiety having a substitutable or a bond-forming position.

7. The method of Claim 6 wherein said monocyclic heterocyclic moiety of Formula IIa is selected from thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl, isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl, 1,4-pyranyl, 1,2-pyronyl, 1,4-pyronyl, pyridinyl, piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,3,6-

oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl, 1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

8. The method of Claim 7 wherein said bicyclic heterocyclic moiety of Formula IIb is selected from benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl, 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiolo-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and 4H-1,3-dioxolo[4,5-d]imidazolyl.

9. The method of Claim 8 wherein said angiotensin II receptor antagonist compound having said first-and-second-portion moieties of Formula I and II is further characterized by having an acidic moiety attached to either of said first-and-second-portion moieties.

10. The method of Claim 9 wherein said acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:

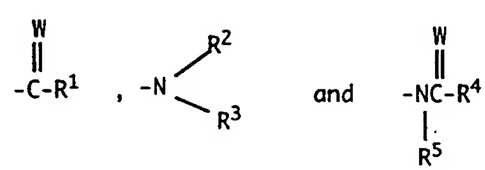
$$-U_nA \qquad \text{(III)}$$

wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties;

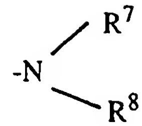
wherein U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms.

11. The method of Claim 10 wherein said acidic moiety is selected from carboxyl moiety and tetrazolyl moiety.

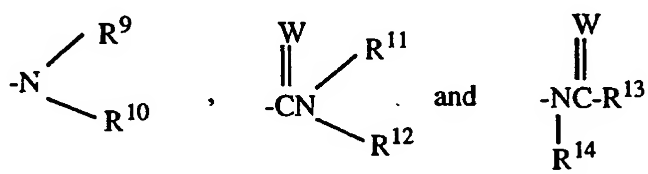
12. The method of Claim 10 wherein any of the moieties of Formula I and Formula II may be substituted at any substitutable position by one or more radicals selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



wherein W is oxygen atom or sulfur atom; wherein each of R^1 through R^5 is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR^6 and



wherein Y is selected from oxygen atom and sulfur atom and R^6 is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^1, R^2, R^3, R^4, R^5, R^7 and R^8 is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^1, R^2, R^3, R^4, R^5, R^7 and R^8 is further independently selected from amino and amido radicals of the formula



wherein W is oxygen atom or sulfur atom; wherein each of R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^2 and R^3 taken together and each of R^4 and R^5 taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein each of R^2 and R^3 taken together and each of R^7 and R^8 taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido

radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

13. The method of Claim 12 wherein said angiotensin II receptor antagonist is 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole or a pharmaceutically-acceptable salt thereof and said epoxy-steroidal aldosterone receptor antagonist is
9α-,11α-epoxy-7α-methoxycarbonyl-20-spirox-4-ene-3,21-dione or a pharmaceutically-acceptable salt thereof.

14. The method of Claim 13 further characterized by said angiotensin II receptor antagonist and said epoxy-steroidal aldosterone receptor antagonist being present in said combination in a weight ratio range from about one-to-one to about twenty-to-one of said angiotensin II receptor antagonist to said aldosterone receptor antagonist.

15. The method of Claim 14 wherein said weight ratio range is from about five-to-one to about fifteen-to-one.

16. The method of Claim 15 wherein said weight ratio range is about ten-to-one.

17. The method of Claim 1 wherein said angiotensin II receptor antagonist is selected from the group consisting of:
saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22,

WAY-126227, WK-1492.2K, YM-31472, losartan potassium, E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234, L-162441, L-163007, PD-123177, A-81988, BMS-180560, CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167, EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline, KRI-1177, L-158809, L-158978, L-159874, LR B087, LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, saprisartan, saralasin, Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731, BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017, LY-301875, XH-148, XR-510, zolasartan and PD-123319.

18. The method of Claim 17 wherein said angiotensin II receptor antagonist is selected from the group consisting of:
saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22, WAY-126227, WK-1492.2K, YM-31472, losartan potassium, E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234, L-162441, L-163007 and PD-123177.

19. The method of Claim 1 comprising administering said combination to treat or prevent the progression of cardiofibrosis.

20. The method of Claim 1 comprising administering said combination to treat or prevent the progression of cardiac hypertrophy.

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(54) Title: METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST

(57) Abstract

A therapeutic method is described for treating cardiofibrosis or cardiac hypertrophy using a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compounds characterized by the presence of a 9α,11α-substituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/08709

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/585 A61K45/06 A61K31/41 //(A61K45/06,31:585), (A61K45/06,31:41)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,94 09778 (MERCK & CO LTD) 11 May 1994 see page 1-2; figures I-XI	1-20
A	see page 6, line 9; claims 1-3,5-8,10	14-16

Y	WO,A,91 15206 (DU PONT DE NEMOURS; MERCK & CO) 17 October 1991	1-20
A	see page 21, line 12-20; claims 1-4,6-8 see page 24, line 7-12 see page 24, line 19-30 see page 26, line 1-6	14

Y	EP,A,0 481 448 (SQUIBB & SONS INC.) 22 April 1992	1-20
A	see page 11, line 20-45; claims 1,6-8,12,13; examples 12-21	13,17,18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 1996	06.12.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Kanbier, D

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO,A,91 12001 (MERCK & CO INC) 22 August 1991	1-20
A	see page 167	13,17,18

Y	THE JOURNAL OF STEROID BIOCHEMISTRY, vol. 32, no. 1b, 1989, pages 223-227, XP000607722 DE GASPARO ET AL: "ANTIALDOSTERONES: INCIDENCE AND PREVENTION OF SEXUAL SIDE EFFECTS" see page 223, right-hand column see page 225	1-20
A	see page 226, right-hand column	13

P,Y	WO,A,95 15166 (CURATORS OF THE UNIVERSITY OF MISSOURI) 8 June 1995	1-20
P,A	see page 8-12; claims 1,3 see page 14	13-16

A	THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 240, no. 2, 1987, pages 650-656, XP000607709 DE GASPARO ET AL: "THREE NEW EPOXY-SPIROLACTONE DERIVATIVES: CHARACTERIZATION IN VIVO AND IN VITRO" see page 650 see page 653, left-hand column see page 654	1-5,19, 20

A	EP,A,0 122 232 (CIBA-GEIGY AG) 17 October 1984 see page 3, paragraph 5 - page 5, paragraph 4; claims 1-8,10 see page 21, paragraph 2 - page 22, paragraph 1; example 17	1-5

1

INTERNATIONAL SEARCH REPORT	International application No. PCT/US 96/08709

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-20 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

Please see next page

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FR M PCT/ISA/210

In view of the large number of compounds, which are defined by the general formula/description, used in claims 2, 6-12, 17, 18, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application (see Guidelines, part B, chapter III, paragraph 3.6).

A compound cannot be sufficiently characterized by its pharmacological profile or its mechanism of action as it is done in claim 1 as: "angiotensin II receptor antagonist" and a "aldosterone receptor antagonist". The search has been executed based on compounds specifically mentioned in claims 3-5, 13 and in the examples

Claims searched incompletely: 1, 2, 6-12, 17, 18

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ·ional Application No
PCT/US 96/08709

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